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(57) Abstract

The invention provides human proteins having transmembrane domains and cDNAs coding for these proteins as well as eukaryotic cells expressing said cDNAs. All of the proteins exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins can be employed as pharmaceuticals such as carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against said proteins. The cDNAs can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized for large-scale expression of said proteins. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low-molecular pharmaceuticals, and so on.

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DESCRIPTION

Human Proteins Having Transmembrane
Domains and DNAs Encoding these Proteins

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TECHNICAL FIELD

The present invention relates to human proteins having transmembrane domains and cDNAs coding for these proteins as well as eucaryotic cells expressing said cDNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against said proteins. The human cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by said cDNAs. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low-molecular pharmaceuticals, and so on.

20

BACKGROUND ART

Membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. in the material transportation and the information transmission which are mediated by the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino

acids, and so on, where the genes of many of them have been cloned already.

It has been clarified that abnormalities of these membrane proteins are associated with a number of hitherto-cryptogenic diseases. For instance, a gene of a membrane protein having twelve transmembrane domains was identified as the gene responsible for cystic fibrosis [Rommens, J. M. et al., Science 245: 1059-1065 (1989)]. In addition, it has been clarified that several membrane proteins act as receptors when a virus infects the cells. For instance, HIV-1 is revealed to infect into the cells through mediation of a membrane protein fusin having a membrane protein on the T-cell membrane, a CD-4 antigen, and seven transmembrane domains [Feng, Y. et al., Science 272: 872-877 (1996)]. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification, many membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises transfection of a cDNA library in eucaryotic cells to express cDNAs and then detection of the cells expressing the target membrane protein on the membrane by an immunological technique using an antibody or a physiological technique on the change in the membrane permeability. However, this method is applicable only to cloning of a gene of a membrane protein with a known function.

In general, membrane proteins possess hydrophobic transmembrane domains inside the proteins, wherein, after

synthesis thereof in the ribosome, these domains remain in the phospholipid membrane to be trapped in the membrane. Accordingly, the evidence of the cDNA for encoding the membrane protein is provided by determination of the whole base sequence of a
5 full-length cDNA followed by detection of highly hydrophobic transmembrane domains in the amino acid sequence of the protein encoded by said cDNA.

DISCLOSURE OF INVENTION

10 The object of the present invention is to provide novel human proteins having transmembrane domains and DNAs coding for said proteins as well as transformation eucaryotic cells that are capable of expressing said cDNAs.

As the result of intensive studies, the present inventors
15 have been successful in cloning of cDNAs coding for proteins having transmembrane domains from the human full-length cDNA bank, thereby completing the present invention. In other words, the present invention provides human proteins having transmembrane domains, namely proteins containing any of the amino acid
20 sequences represented by Sequence Nos. 1 to 10. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs containing any of the base sequences represented by Sequence Nos. 11 to No. 20, as well as transformation eucaryotic cells that are capable of expressing
25 said cDNAs.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01244.

5 Figure 2: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01498.

Figure 3: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by
10 clone HP01565.

Figure 4: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01606.

Figure 5: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by
15 clone HP01737.

Figure 6: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01962.

20 Figure 7: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10435.

Figure 8: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by
25 clone HP10479.

Figure 9: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by

clone HP10481.

Figure 10: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10495.

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BEST MODE FOR CARRYING OUT OF THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical
10 synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the transmembrane domains of the present invention, wherein the method for obtainment by the recombinant DNA technology is employed preferably. For instance, in vitro expression of the proteins can be achieved by
15 preparation of an RNA by in vitro transcription from a vector having one of cDNAs of the present invention, followed by in vitro translation using this RNA as a template. Also, recombination of the translation region into a suitable expression vector by the method known in the art leads to production of a large amount of
20 the encoded protein by using prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case in which a protein of the present invention is produced by a microorganism such as *Escherichia coli* etc., a
25 recombinant expression vector bearing the translation region in the cDNA of the present invention is constructed in an expression vector having an origin, a promoter, a ribosome-binding site, a

cdNA-cloning site, a terminator etc., which can be replicated in the microorganism, and, after transformation of the host cells with said expression vector, the thus-obtained transformant is incubated, whereby the protein encoded by said cdNA can be produced
5 on a large scale in the microorganism. In this case, a protein fragment containing an optional region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind an optional translation region. Alternatively, a fusion protein with another protein can
10 be expressed. Only a protein portion coding for said cdNA can be obtained by cleavage of said fusion protein with a suitable protease.

In the case in which one of the proteins of the present invention is produced in eucaryotic cells, the protein of the
15 present invention can be produced as a transmembrane protein on the cell-membrane surface, when the translation region of said cdNA is subjected to recombination to an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) insertion site, etc., followed by introduction into the eucaryotic
20 cells. The expression vector is exemplified by pKA1, Ped6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian culture cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, etc., budding yeasts, fission
25 yeasts, silkworm cells, *Xenopus laevis* egg cells, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the present proteins on the membrane surface. The

expression vector can be introduced in the eucaryotic cells by methods known in the art such as the electroporation method, the potassium phosphate method, the liposome method, the DEAE-dextran method, and so on.

5 After one of the proteins of the present invention is expressed in prokaryotic cells or eucaryotic cells, the objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea
10 or a surface-active agent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

15 The proteins of the present invention include peptide fragments (more than 5 amino acid residues) containing any partial amino acid sequence in the amino acid sequences represented by Sequence Nos. 1. to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Hereupon, among the
20 proteins of the present invention, those having the signal sequence are secreted in the form of maturation proteins on the surface of the cells, after the signal sequences are removed. Therefore, these maturation proteins shall come within the scope of the present invention. The N-terminal amino acid sequences of
25 the maturation proteins can be easily identified by using the method for the cleavage-site determination in a signal sequence [Japanese Patent Kokai Publication No. 1996-187100]. Furthermore,

some membrane proteins undergo the processing on the cell surface to be converted to the secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. When sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins wherein sugar chains are added. Accordingly, such proteins or peptides wherein sugar chains are added shall come within the scope of the present invention.

The DNAs of the present invention include all DNAs coding for the above-mentioned proteins. Said DNAs can be obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries of the human cell origin. These cDNA are synthesized by using as templates poly(A)⁺ RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the culture cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner.

The primary selection of one of the cDNAs coding for the human proteins having transmembrane domains is carried out by sequencing of a partial base sequence of a cDNA clone selected

at random from cDNA libraries, sequencing of the amino acid sequence encoded by the base sequence, and recognition of the presence or absence of a hydrophobic site in the resulting N-terminal amino acid sequence region. Next, the secondary selection

5. is carried out by determination of the whole sequence by the sequencing and the protein expression by in vitro translation. Ascertainment of cDNAs of the present invention for encoding the proteins having secretory signal sequences is carried out by using the signal sequence detection method [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)]. In other words, the ascertainment for a coding portion of an inserted cDNA fragment to function as a signal sequence is provided by fusing a cDNA fragment coding for the N-terminus of the target protein with a cDNA coding for the protease domain of urokinase and then expressing the resulting
10 cDNA in COS7 cells to detect the urokinase activity in the cell culture medium. On the other hand, in the case in which the urokinase activity is not detectable in the cell medium, the N-terminal region is judged to remain in the membrane.

The cDNAs of the present invention are characterized by containing
20 either of the base sequences represented by Sequence Nos. 11 to 20 or the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Table 1 summarizes the clone number (HP number), the cells affording the cDNA, the total base number of the cDNA, and the number of the amino acid residues of the encoded
25 protein, for each of the cDNAs.

Table 1

	Sequence No.	HP No.	Cell	Number of bases	Number of amino acids
5	1, 11, 21	HP 01244	Stomach Cancer	979	123
	2, 12, 22	HP 01498	Stomach Cancer	1279	220
	3, 13, 23	HP 01565	Stomach Cancer	835	81
	4, 14, 24	HP 01606	Stomach Cancer	1256	301
10	5, 15, 25	HP 01737	Stomach Cancer	1305	383
	6, 16, 26	HP 01962	Liver	899	199
	7, 17, 27	HP 10435	Stomach Cancer	905	229
	8, 18, 28	HP 10479	PMA-U937	841	178
	9, 19, 29	HP 10481	PMA-U937	1451	443
15	10, 20, 30	HP 10495	Stomach Cancer	886	130

Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines and human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 35, 37 and 39.

In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA that is subjected to insertion or deletion of one or plural nucleotides and/or substitution with other nucleotides in Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 35, 37 and 39 shall come within the scope of the present invention.

In a similar manner, any protein that is formed by these modifications comprising insertion or deletion of one or plural amino acids and/or substitution with other amino acids shall come

within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by Sequence Nos. 1 to 10.

The cDNAs of the present invention include cDNA fragments
5 (more than 10 bp) containing any partial base sequence in the base sequences represented by Sequence Nos. 11 to 20 or in the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 30, 31, 33, 35 and 39. Also, DNA fragments consisting of a sense chain and an anti-sense chain shall come within this scope. These DNA
10 fragments can be utilized as the probes for the gene diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses
15 or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

20 Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for
25 tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as

molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to
5 hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip"
10 or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such
15 as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding
20 interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune
25 response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a

particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to
5 the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may
10 induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of
15 a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

20 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies,
25 E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in

Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 5 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in 10 Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferony, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

15 Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 20 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. 25 J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett,

F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and
5 Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring
10 proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse
15 Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

20 Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune
25 deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting

the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may

be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a

monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject.

Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development

of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune

responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of

the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected
5 ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected
10 cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells
15 to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a
20 cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with
25 a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an

antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. *Immunol.* 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Bertagnolli et al., *J. Immunol.* 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., *J. Immunol.* 134:536-544, 1995; Inaba et al., *Journal of Experimental Medicine* 173:549-559, 1991; Macatonia et al., *Journal of Immunology* 154:5071-5079, 1995; Porgador et al., *Journal of Experimental Medicine* 182:255-260, 1995; Nair et al., *Journal of Virology* 67:4062-4069, 1993; Huang et al., *Science* 264:961-965, 1994; Macatonia et al., *Journal of Experimental*

Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will
5 identify, among others, proteins that prevent apoptosis after
superantigen induction and proteins that regulate lymphocyte
homeostasis) include, without limitation, those described in:
Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al.,
Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research
10 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk,
Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry
14:891-897, 1993; Gorczyca et al., International Journal of
Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell
15 commitment and development include, without limitation, those
described in: Antica et al., Blood 84:111-117, 1994; Fine et al.,
Cellular Immunology 155:111-122, 1994; Galy et al., Blood
85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA
88:7548-7551, 1991.

20 Hematopoiesis Regulating Activity

A protein of the present invention may be useful in
regulation of hematopoiesis and, consequently, in the treatment
of myeloid or lymphoid cell deficiencies. Even marginal
biological activity in support of colony forming cells or of
25 factor-dependent cell lines indicates involvement in regulating
hematopoiesis, e.g. in supporting the growth and proliferation
of erythroid progenitor cells alone or in combination with other

cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lymphohematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns,
5 incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such
10 a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced
15 craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells,
20 stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of
25 tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may

be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally
5 formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue,
10 as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or
15 ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce
20 differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament
25 defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part

of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

5 A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

10 A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

15 Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

20 Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

25 A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating

hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful
5 as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with
10 other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for
15 advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

20 Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

25 Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian

cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired
5 site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune
10 responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability
15 to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other
20 means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce
25 the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology,

Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 5 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

10 A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds 15 resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

20 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 25 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their
5 ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen
10 presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of
15 receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include
20 without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al.,
25 Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods

175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may
5 be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by
10 stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such
15 as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of
20 cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for
25 immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may

inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

Other Activities

10 A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily
15 characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms;
20 effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including,
25 without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders)

and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting
5 deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an
10 immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

The present invention is embodied in more detail by the
15 following examples, but this embodiment is not intended to restrict the present invention. The basic operations and the enzyme reactions with regard to the DNA recombination are carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise
20 stated, restrictive enzymes and a variety of modification enzymes to be used were those available from TAKARA SHUZO. The manufacturer's instructions were used for the buffer compositions as well as for the reaction conditions, in each of the enzyme reactions. The cDNA synthesis was carried out according to the
25 literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Preparation of Poly(A)⁺ RNA

The histiocyte lymphoma cell line U937 (ATCC CRL 1593)

stimulated by phorbol ester, tissues of stomach cancer delivered by the operation, and the liver were used for human cells to extract mRNAs. The cell line was incubated by a conventional procedure.

After about 1 g of the human cells was homogenized in 20 ml of a 5.5 M guanidinium thiocyanate solution, a total mRNA was prepared according to the literature [Okayama, H. et al., "Method in Enzymology", Vol. 164, Academic Press, 1987]. This was subjected to chromatography on oligo(dT)-cellulose column washed with a 20 mM Tris-hydrochloride buffer solution (pH 7.6), 0.5 M NaCl, and 1 mM EDTA to obtain a poly(A)⁺ RNA according to the above-described literature.

(2) Construction of cDNA Library

Ten micrograms of the above-mentioned poly(A)⁺ RNA were dissolved in a 100 mM Tris-hydrochloride buffer solution (pH 8), one unit of an RNase-free, bacterial alkaline phosphatase was added, and the reaction was run at 37°C for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 50 mM sodium acetate (pH 6), 1 mM EDTA, 0.1% 2-mercaptoethanol, and 0.01% Triton X-100. Thereto was added one unit of a tobacco-origin acid pyrophosphatase (Epicentre Technologies) and a total 100 µl volume of the resulting mixture was reacted at 37°C for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in water to obtain a solution of a decapped poly(A)⁺ RNA.

The decapped poly(A)⁺ RNA and 3 nmol of a chimeric DNA-

RNA oligonucleotide (5'-dG-dG-dG-dG-dA-dA-dT-dT-dC-dG-dA-G-G-A-3') were dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 7.5), 0.5 mM ATP, 5 mM MgCl₂, 10 mM 2-mercaptoethanol, and 25% polyethylene glycol, where to was added 50 units of T4RNA ligase and a total 30 µl volume of the resulting mixture was reacted at 20°C for 12 hours. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in water to obtain a chimeric-oligo-capped poly(A)* RNA.

10 After digestion of vector pKA1 (Japanese Patent Kokai Publication No. 1992-117292) developed by the present inventors with KpnI, about 60 dT tails were added using a terminal transferase. A vector primer to be used below was prepared by digestion of this product with EcoRV to remove a dT tail at one side.

15 After 6 µg of the previously-prepared chimeric-oligo-capped poly(A)* RNA was annealed with 1.2 µg of the vector primer, the resulting product was dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 8.3), 75 mM KCl, 3 mM MgCl₂, 10 mM dithiothreitol, and 1.25 mM dNTP (dATP + dCTP + dGTP + dTTP), 200 units of a reverse transcriptase (GIBCO-BRL) were added, and the reaction in a total 20 µl volume was run at 42°C for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 7.5), 100 mM NaCl, 10 mM MgCl₂, and 1 mM dithiothreitol. Thereto were added 100 units of EcoRI and a total 20 µl volume of the resulting mixture was reacted at

25

37°C for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 20 mM Tris-hydrochloride buffer solution (pH 7.5), 100 mM KCl, 4 mM MgCl₂,
5 10 mM (NH₄)₂SO₄, and 50 µg/ml of the bovine serum albumin. Thereto were added 60 units of an *Escherichia coli* DNA ligase and the resulting mixture was reacted at 16°C for 16 hours. To the reaction solution were added 2 µl of 2 mM dNTP, 4 units of *Escherichia coli* DNA polymerase I, and 0.1 unit of *Escherichia coli* RNase H and
10 the resulting mixture was reacted at 12°C for one hour and then at 22°C for one hour.

Next, the cDNA-synthesis reaction solution was used for transformation of *Escherichia coli* DH12S (GIBCO-BRL). The transformation was carried out by the electroporation method. A
15 portion of the transformant was sprayed on the 2xYT agar culture medium containing 100 µg/ml ampicillin and the mixture was incubated at 37°C overnight. A colony formed on the agar medium was picked up at random and inoculated on 2 ml of the 2xYT culture medium containing 100 µg/ml ampicillin. After incubation at 37°C
20 overnight, the culture mixture was centrifuged to separate the mycelia, from which a plasmid DNA was prepared by the alkaline lysis method. The plasmid DNA was subjected to double digestion with EcoRI and NotI, followed by 0.8% agarose gel electrophoresis, to determine the size of the cDNA insert. Furthermore, using the
25 thus-obtained plasmid as a template, the sequence reaction was carried out by using an M13 universal primer labeled with a fluorescent dye and a Taq polymerase (a kit of Applied Biosystems)

and then the product was examined with a fluorescent DNA sequencer (Applied Biosystems) to determine an about 400-bp base sequence at the 5'-terminus of the cDNA. The sequence data were filed as the homo/protein cDNA bank database.

5 (3) Selection of cDNAs Encoding Proteins Having Transmembrane Domains

A base sequence registered in the homo/protein cDNA bank was converted to three frames of amino acid sequences and the presence or absence of an open reading frame (ORF) beginning from
10 the initiation codon was examined. Then, the selection was made for the presence of a signal sequence that is characteristic to a secretory protein at the N-terminus of the portion encoded by the ORF. These clones were sequenced from the both 5' and 3' directions by the use of the deletion method using exonuclease
15 III to determine the whole base sequence. The hydrophobicity/hydrophilicity profiles were obtained for proteins encoded by the ORF by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. In the case in
20 which there is a hydrophobic region of a putative transmembrane domain in the amino acid sequence of an encoded protein, this protein was judged as a membrane protein.

(4) Functional Verification of Secretory Signal Sequence or Transmembrane Domains

25 It was verified by the method described in the literature [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)] that the N-terminal hydrophobic region in the secretory protein clone

candidate obtained in the above-mentioned steps functions as a secretory signal sequence. First, the plasmid containing the target cDNA was cleaved at an appropriate restriction enzyme site existing at the downstream of the portion expected for encoding
5 the secretory signal sequence. In the case in which this restriction site was a protruding terminus, the site was blunt-ended by the Klenow treatment or treatment with the mung-bean nuclease. Digestion with HindIII was further carried out and a DNA fragment containing the SV40 promoter and a cDNA
10 encoding the secretory signal sequence at the downstream of the promoter was separated by agarose gel electrophoresis. The resulting fragment was inserted between HindIII in pSSD3 (DDBJ/EMBL/GenBank Registration No. AB007632) and a restriction enzyme site selected so as to match with the urokinase-coding frame,
15 thereby constructing a vector expressing a fusion protein of the secretory signal sequence of the target cDNA and the urokinase protease domain.

After *Escherichia coli* (host: JM109) bearing the fusion-protein expression vector was incubated at 37°C for 2 hours
20 in 2 ml of the 2xYT culture medium containing 100 µg/ml of ampicillin, the helper phage M13KO7 (50 µl) was added and the incubation was continued at 37 °C overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles.
25 These particles were suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE). Also, there were used as controls suspensions of single-stranded phage particles prepared in the same manner from

pSSD3 and from the vector pKAl-UPA containing a full-length cDNA of urokinase [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)].

The culture cells originating from the simian kidney, COS7,
5 were incubated at 37°C in the presence of 5% CO₂ in the Dulbecco's modified Eagle's culture medium (DMEM) containing 10% fetal calf albumin. Into a 6-well plate (Nunc Inc., 3 cm in the well diameter) were inoculated 1×10^5 COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO₂. After the culture
10 medium was removed, the cell surface was washed with a phosphate buffer solution and then washed again with DMEM containing 50 mM Tris-hydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM culture medium, and 3 µl of
15 TRANSFECTAM™ (IBF Inc.) and the resulting mixture was incubated at 37°C for 3 hours in the presence of 5% CO₂. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf albumin was added, and the incubation was carried out at 37°C for 2 days in the presence
20 of 5% CO₂.

To 10 ml of 50 mM phosphate buffer solution (pH 7.4) containing 2% bovine fibrinogen (Miles Inc.), 0.5% agarose, and 1 mM calcium chloride were added 10 units of human thrombin (Mochida Pharmaceutical Co., Ltd.) and the resulting mixture was solidified
25 in a plate of 9 cm in diameter to prepare a fibrin plate. Ten microliters of the culture supernatant of the transfected COS7 cells were spotted on the fibrin plate, which was incubated at

37°C for 15 hours. In the case in which a clear circle appears on the fibrin plate, it is judged that the cDNA fragment codes for the amino acid sequence functioning as a secretory signal sequence. On the other hand, in case in which a clear circle is not formed, the cells were washed well, then the fibrin sheet was placed on the cells, and incubation was carried out at 37°C for 15 hours. In case in which a clear portion is formed on the fibrin sheet, it indicates that the urokinase activity was expressed on the cell surface. In other words, the cDNA fragment is judged to code for the transmembrane domains.

(5) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T₇T rabbit reticulocyte lysate kit (Promega). In this case, [³⁵S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was reacted at 30°C for 90 minutes in a total 25 µl volume of the reaction solution containing 12.5 µl of T₇T rabbit reticulocyte lysate, 0.5 µl of a buffer solution (attached to kit), 2 µl of an amino acid mixture (methionine-free), 2 µl of [³⁵S]methionine (Amersham) (0.37 MBq/µl), 0.5 µl of T7RNA polymerase, and 20 U of RNasin. To 3 µl of the resulting reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel

electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiograph.

(6) Expression by COS7

Escherichia coli bearing the expression vector of the protein of the present invention was infected with helper phage M13KO7 and single-stranded phage particles were obtained by the above-mentioned procedure. The thus-obtained phage was used for introducing each expression vector in the culture cells originating from the simian kidney, COS7. After incubation at 37°C for 2 days in the presence of 5% CO₂, the incubation was continued for one hour in the culture medium containing [³⁵S]cystine or [³⁵S]methionine. Collection and dissolution of the cells, followed by subjecting to SDS-PAGE, allowed to observe the presence of a band corresponding to the expression product of each protein, on the membrane fraction which did not exist in the COS7 cells. For instance, the molecular weights of HP01498, HP01565, HP01737, HP010435 and HP010495 were respectively 20 kDa, 13 kDa, 52 kDa, 33 kDa and 20 kDa.

(7) Clone Examples

<HP01244> (Sequence Nos. 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP01244 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 15-bp 5'-nontranslation region, a 372-bp ORF, and a 592-bp 3'-nontranslation region. The ORF codes for a protein consisting of 123 amino acid residues and there existed a signal-like sequence at the N-terminus and one transmembrane domain at the C-terminal.

Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 14 kDa that was almost consistent with the molecular weight of 12,911 predicted from the ORF.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the chicken stem cell antigen 2 (GenBank Accession No. L34554). Table 2 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the chicken stem cell antigen 2 (GG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 33.9% in the entire region.

Table 2

	HS MKAVLLALLMAGLALQPGTALLCYSCKAQVSNEDCLQVKNTQLGEQCWTA--RIRAVGL
20	*** *.*.* * * *.*.**... ** ** .*. .*. * * . *
	GG MKAFLFAVLAAVLCVERAHTLICFSCSDASSNWACLTPVKCAENEHCVTITYVGVGIGGK
	HS LT-VISKGCSLNCVDDSQDYVVGKKNITCCDTLNCASGAHALQAAAIAL--LPALGL
	. ***** * ***. *** **. *.*** * ..
	GG SGQSISKGCSPVCPSAGINLGIAAASVYCCDSFLCNISGSSSVKASYAVLALGILVSFVY
25	HS LLWGPQQL
	.*..
	GG VLRARE

30 Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of

sequences that possessed a homology of 90% or more (for example, Accession No. AA476643) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found. <HP01498> (Sequence Nos. 2, 12, and 23)

5 Determination of the whole base sequence of the cDNA insert of clone HP01498 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 227-bp 5'-nontranslation region, a 663-bp ORF, and a 389-bp 3'-nontranslation region. The ORF codes for a protein consisting of
10 220 amino acid residues and there existed four transmembrane domains. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost consistent with the
15 molecular weight of 23,318 predicted from the ORF.

 The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the rat protein RVP1 (NBRF Accession No. A39484). Table 3 shows the comparison of the amino acid sequence between
20 the human protein of the present invention (HP) and the rat protein RVP1 (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed
25 a homology of 81.8% in the entire region. Hereupon, the rat protein had a sequence longer by 60 amino acid residues at the C-terminal side.

Table 3

HS MSMGLEITGTALAVLGWLGITIVCCALPMWRVSAFIGSNIITSQNIWEGLWMNCVVQSTGQ
 .**.*****.*****.***.*.*****.*****
 5 RN MSMSLEITGTSLAVLGWLGITIVCCALPMWRVSAFIGSSIITAQITWEGLWMNC-VQSTGQ
 HS MQCKVYDSLLALPQDLQAARALIVVAILLAAGLLVALVGAQCTNCVQDDTAKAKITIVA
 ****.*****.*****.*****.*****
 RN MQCKMYDSLLALPQDLQAARALIVVSILLAAGLLVALVGAQCTNCVQDETAKAKITIVA
 HS GVLFLLAALLTLVPVSW SANTIIRDFYNPVPEAQKREMGAGLYVGWAAAALQLLGGALL
 10 *****.*****.*****.*****.*****
 RN GVLFLLA AVLTLVPVSW SANTIIRDFYNPLVPEAQKREMG TGLYVGWAAAALQLLGGALL
 HS CCSCPPREK KYTATKV VYSAPRSTGPGASLGTGYDRKD YV
 ***** **.**.*****. **.***
 RN CCSCPPRE-KYAPTKILYSAPRSTGPGTGTGTAYDRKTTSERPGARTPHHHHYQPSMYPT
 15

Furthermore, the search of the GenBank using the base
 sequences of the present cDNA has revealed the presence of
 sequences that possessed a homology of 90% or more (for example,
 20 Accession No. H72008) in EST, but many sequences were not distinct
 and the same ORF as that in the present cDNA was not found.

The rat protein RVP1 is one of membrane proteins which are
 induced by androgen withdrawal and apoptosis in the rat ventral
 prostate [Briehl, M. M. et al., Mol. Endocrinol. 5: 1381-1388
 25 (1991)]. Accordingly, the present protein is considered to play
 an important role in the signal transduction that is associated
 with apoptosis.

<HP01565> (Sequence Nos. 3, 13, and 25)

Determination of the whole base sequence of the cDNA insert
 30 of clone HP01565 obtained from cDNA libraries of human stomach

cancer revealed the structure consisting of a 62-bp 5'-nontranslation region, a 246-bp ORF, and a 527-bp 3'-nontranslation region. The ORF codes for a protein consisting of 81 amino acid residues and there existed two transmembrane domains.

5 Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost consistent with the molecular weight of 9,374 predicted from the ORF.

10 The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to the nematode putative protein F49C12.13 (GenBank Accession No. Z68227). Table 4 shows the comparison of the amino acid sequence between the human protein
15 of the present invention (HP) and the nematode putative protein F49C12.13 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed
20 a homology of 47.4% in the entire region.

Table 4

HS MAYHGLTVPLIVMSVFVGFVGLVPWFIPKGPNGVIIITMLVTCSVCCYLFWL
*. **. *.**...** **.*****.* *. .***. **. CE MCNFSYFQLQMGILIPLSVSAFWAIIIGFGGPWIVPKGPNGIIQLMIIMTAVCCWMFVI
HS IAILAQLNPLFGPQLKNETIWYLKYHWP
...* *****.***. .**. . .*. CE MVFLHQLNPLIGPQINVKTIRWISEKWGDAPNVIN

10

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. N57319) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01606> (Sequence Nos. 4, 14, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP01606 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 124-bp 5'-nontranslation region, a 906-bp ORF, and a 226-bp 3'-nontranslation region. The ORF codes for a protein consisting of 301 amino acid residues and there existed seven transmembrane domains. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was almost consistent with the molecular weight of 32,594 predicted from the ORF.

The search of the protein data base using the amino acid

sequence of the present protein has revealed the presence of sequences that were analogous to the nematode putative protein F13H11.9 (GenBank Accession No. AF003389). Table 5 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode putative protein F13H11.9 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 45.1% in the region of 195 amino acid residues at the C-terminal side.

Table 5

	HS	MLALRVARGSWGALRGAAWAPGTRPSKRRACWALLPPVPCCLGCLAERWRLRPAALGLRL	
15	CE		MIVTSMFR
	HS	PGIGQRNHCSGAGKAAPRPAAGAGAAAEAPGGQWGPASTPSLYENPWTIPNMLSMTRIGL	
		*..... * . **** . . **.	
	CE	GIACRCELQLLLTPRRMLRNFSLEQKQSPKIESLPPEERGKYKVA-TIPNAICTARIAA	
20	HS	APVLGYLIIIEEDFNIALGVFALAGLTDLLDGFIAARNWANQRSALGSALDPLADKILISIL	
		. *. ***. *. * . . ** ***** . . *. * ***. ***. ***. ***. .	
	CE	TPLIGYLVVQHNFTPAFVLFTVAGATDLLDGFIAARNVPGQKSLGSLVDPVADKLLISTM	
	HS	YVSLTYADLIPVPLTYMIIISRDVMLIAAVFYVRYRTLPTPRTLAKYFNPCYATARLKPTF	
	 ***. ***. ***. . * **. **.. ** **.. * . * . . *** **.	
25	CE	FITMTYAGLIPLPLTSVVILRDICLIGGGFYKRYQVMSPPYSLSRFFNPQVSSMQVVPTM	
	HS	ISKVNTAVQLILVAASLAAPVFNYADSIY--LQILWCFTAFTTAASAYSYYHYGRKTVQV	
		. **. **. . *. ***. **.. ***. * *. *. *** * . *	
	CE	MSKINTVLQITLVALSLSSPVDFSTGANDVIVGLGCITGFTTIYSGLQYASGKAIKKI	

30

Furthermore, the search of the GenBank using the base

sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. C16798) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found.

5 <HP01737> (Sequence Nos. 5, 15, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP01737 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 21-bp 5'-nontranslation region, a 1152-bp ORF, and a 132-bp 3'-nontranslation region. The ORF codes for a protein consisting of 383 amino acid residues and there existed two transmembrane domains. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 45 kDa that was almost consistent with the molecular weight of 43,222 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to the nematode putative protein K09E9.2 (GenBank Accession No. Z79602). Table 6 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode putative protein K09E9.2 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 42.2% in the region of 195 amino acid residues at

the C-terminal side.

Table 6

	HS	MEALGKCLKQFDAYPKTLEDFRVKTCGGATVTIVSGLLMLLLFLSELQYYLTTEVHPELYV
5		*. * . **. ****. *... ***** .*. **..... **.. * . . *. *** .*. *
	CE	MSLLWSLKHFDAYRKPMDDFRVKTLSSGLVTLIATIAIVLLIVLETKQFLSTEVLEHLFV
	HS	D-KSRGDKLKLINIDVLFPHMPCAYLSIDAMDVAGEQQLDVEHNLFKQRLDKDGIPVSSEA
		* *. *. *... **..... *. ****. *. * *** .* .*. *
	CE	DSTTSDERVHIEFDITFTKLPCNFITVDVMDVSSEAQENINDDIYRLRLDPEGRNISESA
10	HS	ERHELKGVEVTVFDPDSLDPDRCESCYGAEAEIDKCCNTCEDVREAYRRRGWAFKNPDTI
		.. *... ..* ..* .. .*. *****. *. * *****. **. ** .**. * ...
	CE	QKIEINQNKTSVETTDVIQEVKCGSCYGAAADGI-CCNTCDDVKSAYAVKGWQV-NIEEV
	HS	EQCRREGFSQKMQEQKNEGCQVYGFLEVNVKAGNFHFAPGKSFQQSHVHVHDLQSFGLDN
	* . **. *** ..* . *****. **. . * . . *****....
15	CE	EQCKNDKWWKEFNEHKNEGCRVYGTVKVAKVAGNFHLAPGDPHQAMRSHVHDLHNLDPVK
	HS	INMTHYIQHLSFGEDYPGIVNPLDHTNVTAPQASMMFQYFVKVPTVYMKVDGEVLRNTQ
		.. * . * . *. ***... ** ***** . ** . *. ***** * . ** * ...*
	CE	FDASHTVNHVSFGKSFPCKNYPLDGKVNTDNRRGIMYQYYVKVPTRYDYLDGRVDQSHQ
	HS	FSVTRHEKVANGLLDGQGLPGVFVLYELSPMMVKLTEKHRSFTHFLTGVCAIIGGMFTVA
20		**** *. * . . . **** *. *. *. *. *. * .. **.. **... ***. *. *. *
	CE	FSVTTHKK--DLGFRQSGLPGFLLQYEFSPLMVQYEEFRQSFASFLVSLCAIVGGVFAMA
	HS	GLIDSLIYHSARAIQKKIDLGKTT
		*. * ****. ** . ** *
	CE	QLVDITIHSSRYMKSRIAGGKLT

25

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. H42261) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

30

<HP01962> (Sequence Nos. 6, 16, and 31)

Determination of the whole base sequence of the cDNA insert of clone HP01962 obtained from cDNA libraries of human liver revealed the structure consisting of a 73-bp 5'-nontranslation
5 region, a 600-bp ORF, and a 226-bp 3'-nontranslation region. The ORF codes for a protein consisting of 199 amino acid residues and there existed at least three transmembrane domains. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro
10 translation resulted in formation of a translation product of 21 kDa that was almost consistent with the molecular weight of 22,134 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of
15 sequences that were analogous to a rat phosphatidylethanolamine N-methyltransferase (SWISS-PROT Accession No. Q08388). Table 7 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the rat phosphatidylethanolamine N-methyltransferase (RN). Therein, the
20 marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 80.8% in the entire region.

Table 7

HS MTRLLGYVDPLDPSFVAAVITITFNPLYWNVVARWEHKTRKLSRAFGSPYLACYSLSVTI
 .. ***** . ***** . ** . *** . ***** . ***** . *
 5 RN SWLLGYVDPTSPFVAAVLTIVFNPLFWNVVARWEQRTRKLSRAFGSPYLACYSLSGSI
 HS LLLNFLRSHCFTQAMLSQPRMESLDTAAAYSLGLALLGLGVVLVLSSFFALGFAGTFLGD
 **** . ***** . *** . ** . ** . . * ***** * . * . ***** . **** . *****
 RN LLLNILRSHCFTQAMMSQPKMEGLDSHTIYFLGLALLGWGLVFLVLSFFYALGFTGTFLGD
 HS YFGILKEARVTVFPFNILDNPMYWGSTANYLGWAIMHASPTGLLLTVLVALTYIVALLYE
 10 ***** . *** . *** . . ***** . ***** . * . **** . *
 RN YFGILKESRVTTFPFSVLDNPMYWGSTANYLGWALMHASPTGLLLTVLVALVYVVALLFE
 HS EPFTAEIYRQKASGSHKRS
 ***** . ** . ****
 RN EPFTAEIYRRKATRLHKRS
 15

Furthermore, the search of the GenBank using the base
 sequences of the present cDNA has revealed the presence of
 sequences that possessed a homology of 90% or more and contained
 20 an initiation codon (for example, Accession No. H83024) in EST,
 but many sequences were not distinct and the same ORF as that in
 the present cDNA was not found.

The rat phosphatidylethanolamine N-methyltransferase is
 a membrane protein which is associated with the biosynthesis of
 25 phosphatidylethanolamine [Cui, Z. et al., J. Biol. Chem. 268:
 16655-16663 (1993)]. The present protein is considered to be a
 human homologue of the phosphatidylethanolamine N-
 methyltransferase and is utilized for the diagnosis and treatment
 of diseases that are associated with abnormalities of this enzyme.
 30 <HP10435> (Sequence Nos. 7, 17, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP10435 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of an 8-bp 5'-nontranslation region, a 690-bp ORF, and a 207-bp 3'-nontranslation region. The ORF codes for a protein consisting of 229 amino acid residues and there existed one transmembrane domain each at the N-terminus and at the C-terminus. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Introduction of an expression vector, wherein the HindIII-BalI fragment containing a cDNA portion coding for the N-terminal 109 amino acid residues of the present protein was inserted into the HindIII-EcoRV site of pSSD3, into the COS7 cells revealed the urokinase activity on the cell surface to indicate that the present protein remains in the membrane. In vitro translation resulted in formation of a translation product of 24 kDa that was almost consistent with the molecular weight of 24,688 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more and contained an initiation codon (for example, Accession No. H87685) in EST, but many sequences were not distinct and the same ORF as that in the present cDNA was not found.

<HP10479> (Sequence Nos. 8, 18, and 35)

Determination of the whole base sequence of the cDNA insert of clone HP10479 obtained from cDNA libraries of the human lymphoma U937 revealed the structure consisting of a 38-bp 5'-nontranslation region, a 537-bp ORF, and a 266-bp 3'-nontranslation region. The ORF codes for a protein consisting of 178 amino acid residues and there existed a signal-like sequence at the N-terminus and one transmembrane domain at the C-terminus. Figure 8 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Introduction of an expression vector, wherein the HindIII-BanII (blunt-ended by treatment with T4DNA polymerase) fragment containing a cDNA portion coding for the N-terminal 45 amino acid residues of the present protein was inserted into the HindIII-SmaI site of pSSD3, into the COS7 cells revealed the urokinase activity in the culture medium to indicate that the present protein is the type-I membrane protein. In vitro translation resulted in formation of a translation product of 33 kDa that was larger than the molecular weight of 19,453 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site in the secretory signal sequence, allows to expect that the maturation protein starts from glutamine at position 22.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to the mouse ion channel homologue RIC (GenBank Accession No. U72680). Table 8 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the mouse ion channel homologue RIC (MM).

Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology
 5 of 48.1% in the entire region.

Table 8

	HS MSPSGRLCLLTIVGLILPTRGQTLKDDTTSSSSADSTIMDIQVPTRAPDAVYTELQPTSPT
10	** *.*****.****.**** *.** ** ***.. ..*.*. .
	MM MSLSSRLCLLTIVALILPSRGQTPKKPTSIFTADQTSATTRDNVPDPDQTS PGVQTTPLI
	HS PTWPADETPQ--PQTQTQLEG-TDGPLVTDPEHKSTKAAHPTDDTTTLSERPSPSTDV
 **.****. ... *.***.*.*. * ... *.***..
	MM WTREEATGSQTAAQTETQQLTKMATSNPVSDPGPHTSSKKGTP---AVSRIEPLSPSKNF
15	HS QTDPTLTKPSGFHEDDPFFYDEHTLRKROLLVAVLFITGIIILTS GKCRQLSRLCRNHC
* .*.**.*. *****.*****.* *
	MM MPPSYIEHPLDSNENNPFFYDDTTLRKROLLVAVLFITGIIILTS GKCRQLSQFCLNRH
	HS R
	*
20	MM R

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of
 25 sequences that possessed a homology of 90% or more (for example, Accession No. AA296696) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

30 The mouse ion channel homologue RIC is one of proteins which are induced on introduction of E2a-Pbx1 oncoprotein into the

NIH3T3 fibroblast cells and has been considered to play an important role in the cell cycle and proliferation [Fu, X. et al., Mol. Cell. Biol. 17: 1503-1512 (1997)].

<HP10481> (Sequence Nos. 9, 19, and 37)

5 Determination of the whole base sequence of the cDNA insert of clone HP10481 obtained from cDNA libraries of the human lymphoma U937 revealed the structure consisting of a 104-bp 5'-nontranslation region, a 1332-bp ORF, and a 15-bp 3'-nontranslation region. The ORF codes for a protein consisting of
10 443 amino acid residues and there existed one transmembrane domain at the N-terminus. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Introduction of an expression vector, wherein the HindIII-PvuII fragment containing
15 a cDNA portion coding for the N-terminal 148 amino acid residues of the present protein was inserted into the HindIII-EcoRV site of pSSD3, into the COS7 cells revealed the urokinase activity on the cell surface to indicate that the present protein is the type-II membrane protein. In vitro translation resulted in formation of
20 a translation product of 51 kDa that was almost consistent with the molecular weight of 51,145 predicted from the ORF.

 The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank
25 using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. AA354554) in EST, but any of the

sequences was shorter than the present cDNAs and was not found to contain the initiation codon.

<HP10495> (Sequence Nos. 10, 20, and 39)

Determination of the whole base sequence of the cDNA insert
5 of clone HP10495 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 62-bp 5'-nontranslation region, a 393-bp ORF, and a 431-bp 3'-nontranslation region. The ORF codes for a protein consisting of
10 domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 25 kDa that was larger than the molecular weight of 14,964 predicted from the ORF.

15 The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more
20 (for example, Accession No. AA431001) in EST, but each of them was shorter than the present cDNA and was not found to contain the initiation codon.

INDUSTRIAL APPLICABILITY

25 The present invention provides human proteins having transmembrane domains and cDNAs coding for these proteins as well as eucaryotic cells expressing said cDNAs. All of the proteins

of the present invention exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as
5 carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against said proteins. The cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be
10 utilized for large-scale expression of said proteins. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low-molecular pharmaceuticals, and so on.

15 The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the
20 genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in
25 accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for

identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism
5 from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense
10 polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference
15 herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic
20 animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s)
25 corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through

deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; 5 Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 10 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the 15 development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is 20 membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and 25 transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-

occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences
5 complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein.
10 Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for
15 example, conditions M-R.

Table 9

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [‡]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
A	DNA : DNA	≥50	65°C: 1×SSC -or- 42°C: 1×SSC.50% formamide	65°C: 0.3×SSC
B	DNA : DNA	<50	T _B *: 1×SSC	T _B *: 1×SSC
C	DNA : RNA	≥50	67°C: 1×SSC -or- 45°C: 1×SSC.50% formamide	67°C: 0.3×SSC
D	DNA : RNA	<50	T _D *: 1×SSC	T _D *: 1×SSC
E	RNA : RNA	≥50	70°C: 1×SSC -or- 50°C: 1×SSC.50% formamide	70°C: 0.3×SSC
F	RNA : RNA	<50	T _F *: 1×SSC	T _F *: 1×SSC
G	DNA : DNA	≥50	65°C: 4×SSC -or- 42°C: 4×SSC.50% formamide	65°C: 1×SSC
H	DNA : DNA	<50	T _H *: 4×SSC	T _H *: 4×SSC
I	DNA : RNA	≥50	67°C: 4×SSC -or- 45°C: 4×SSC.50% formamide	67°C: 1×SSC
J	DNA : RNA	<50	T _J *: 4×SSC	T _J *: 4×SSC
K	RNA : RNA	≥50	70°C: 4×SSC -or- 50°C: 4×SSC.50% formamide	67°C: 1×SSC
L	RNA : RNA	<50	T _L *: 2×SSC	T _L *: 2×SSC
M	DNA : DNA	≥50	50°C: 4×SSC -or- 40°C: 6×SSC.50% formamide	50°C: 2×SSC
N	DNA : DNA	<50	T _N *: 6×SSC	T _N *: 6×SSC
O	DNA : RNA	≥50	55°C: 4×SSC -or- 42°C: 6×SSC.50% formamide	55°C: 2×SSC
P	DNA : RNA	<50	T _P *: 6×SSC	T _P *: 6×SSC
Q	RNA : RNA	≥50	60°C: 4×SSC -or- 45°C: 6×SSC.50% formamide	60°C: 2×SSC
R	RNA : RNA	<50	T _R *: 4×SSC	T _R *: 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C)=81.5 + 16.6(log₁₀[Na⁺]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10.
- 5 2. A DNA coding for the protein according to Claim 1.
3. A cDNA comprising any of the base sequences represented by Sequence Nos. 11 to 20.
4. The cDNA according to Claim 3 comprising any of the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29,
10 31, 33, 35, 37 and 39.
5. A vector capable of expressing the DNA or cDNA according to any of Claims 2 to 4 in in vitro translation or an eucaryotic cell.
6. A transformation eucaryotic cell capable of
15 expressing the DNA or cDNA according to any of Claim 2 to 4 to produce the protein according to Claim 1.

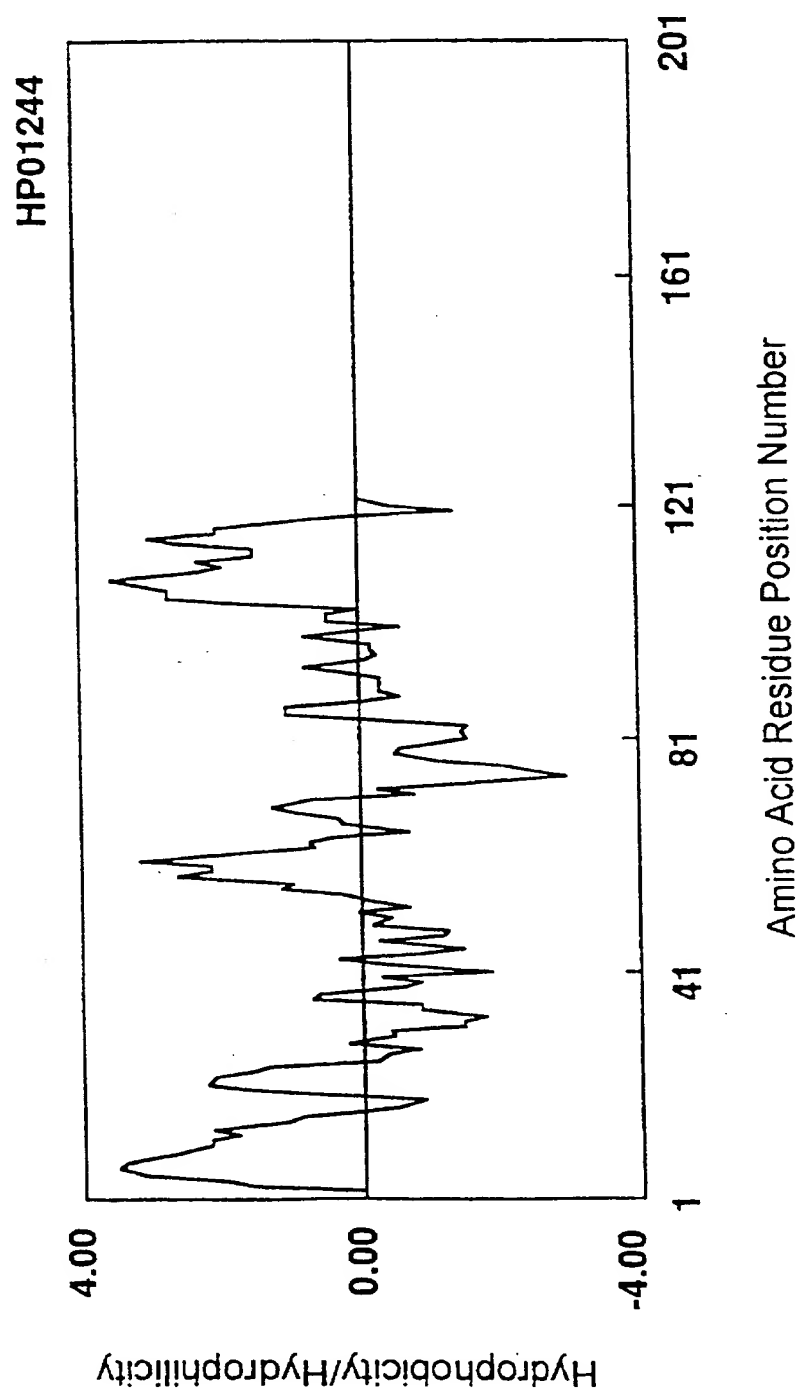


Fig. 1

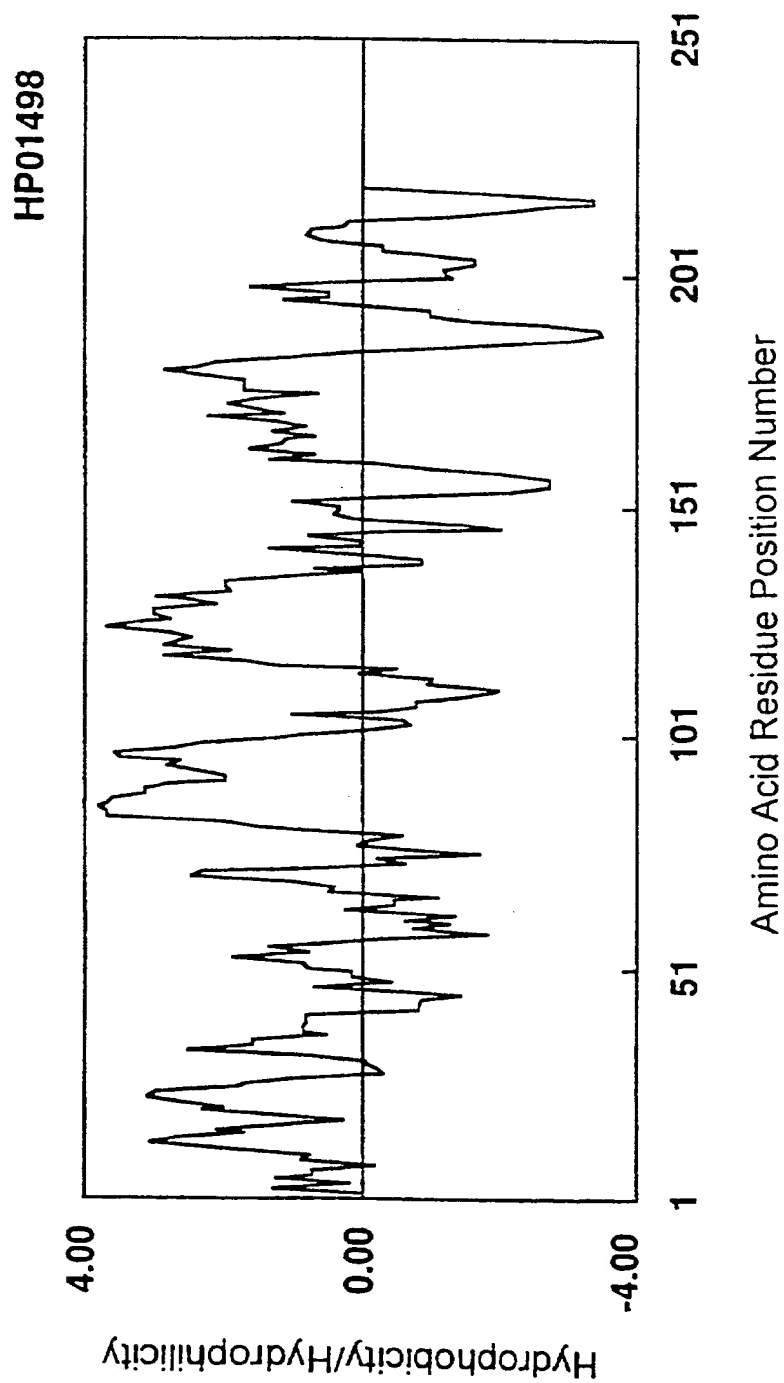


Fig. 2

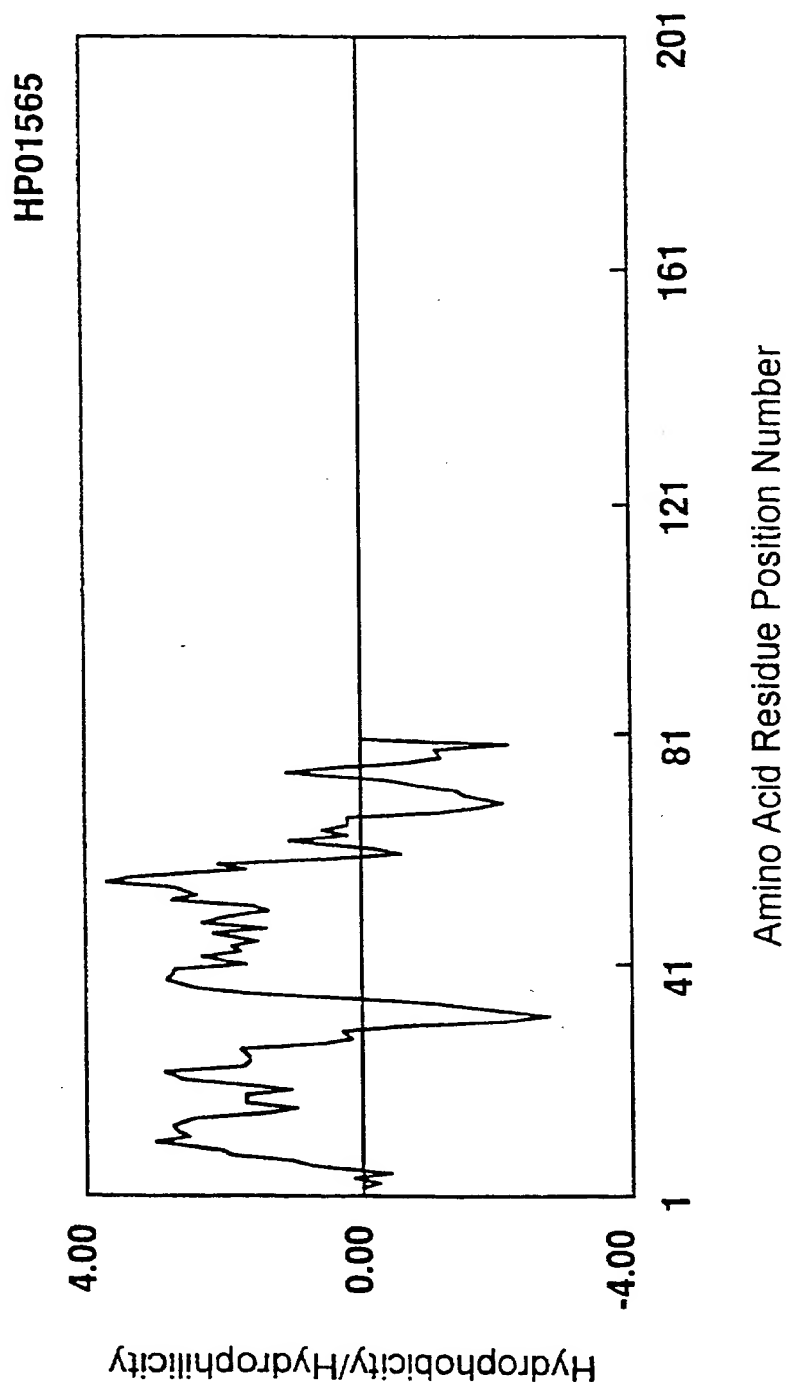


Fig. 3

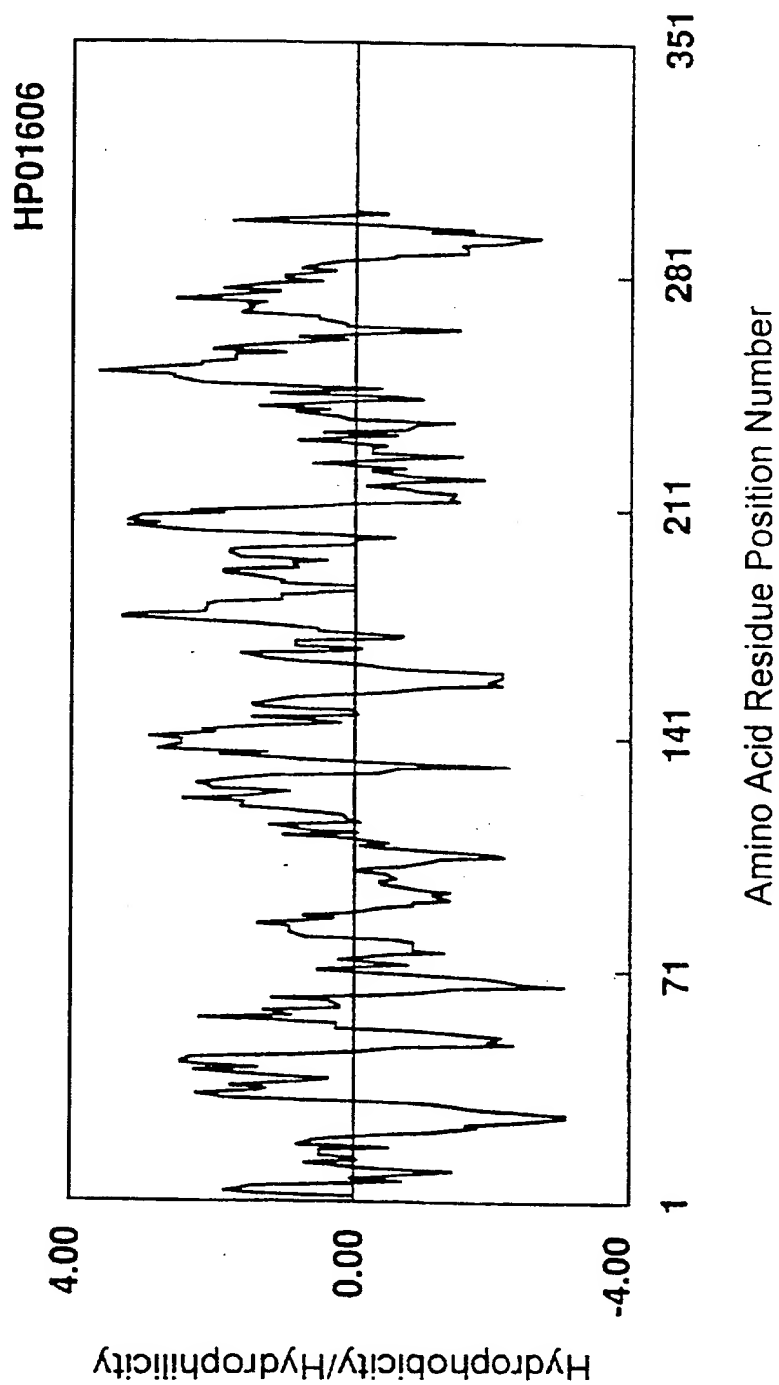


Fig. 4

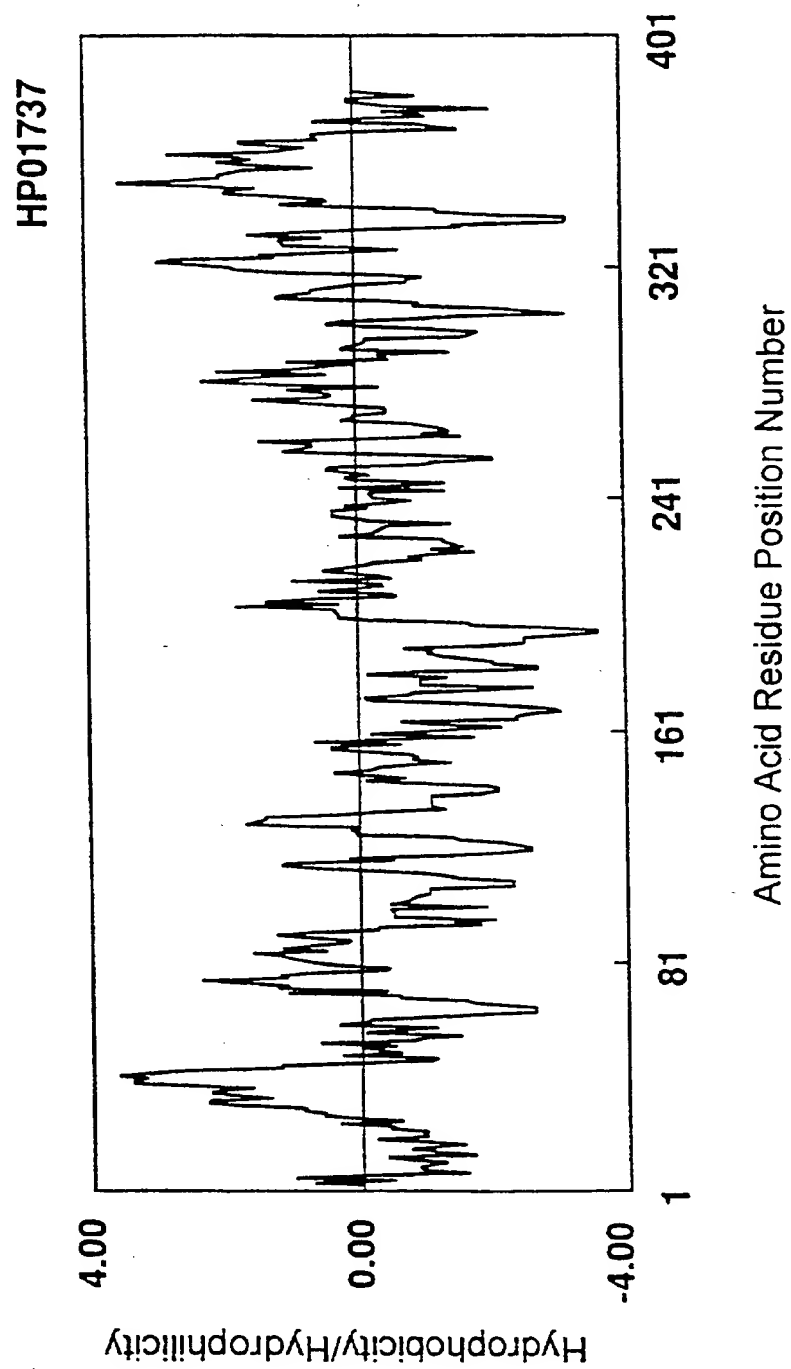


Fig. 5

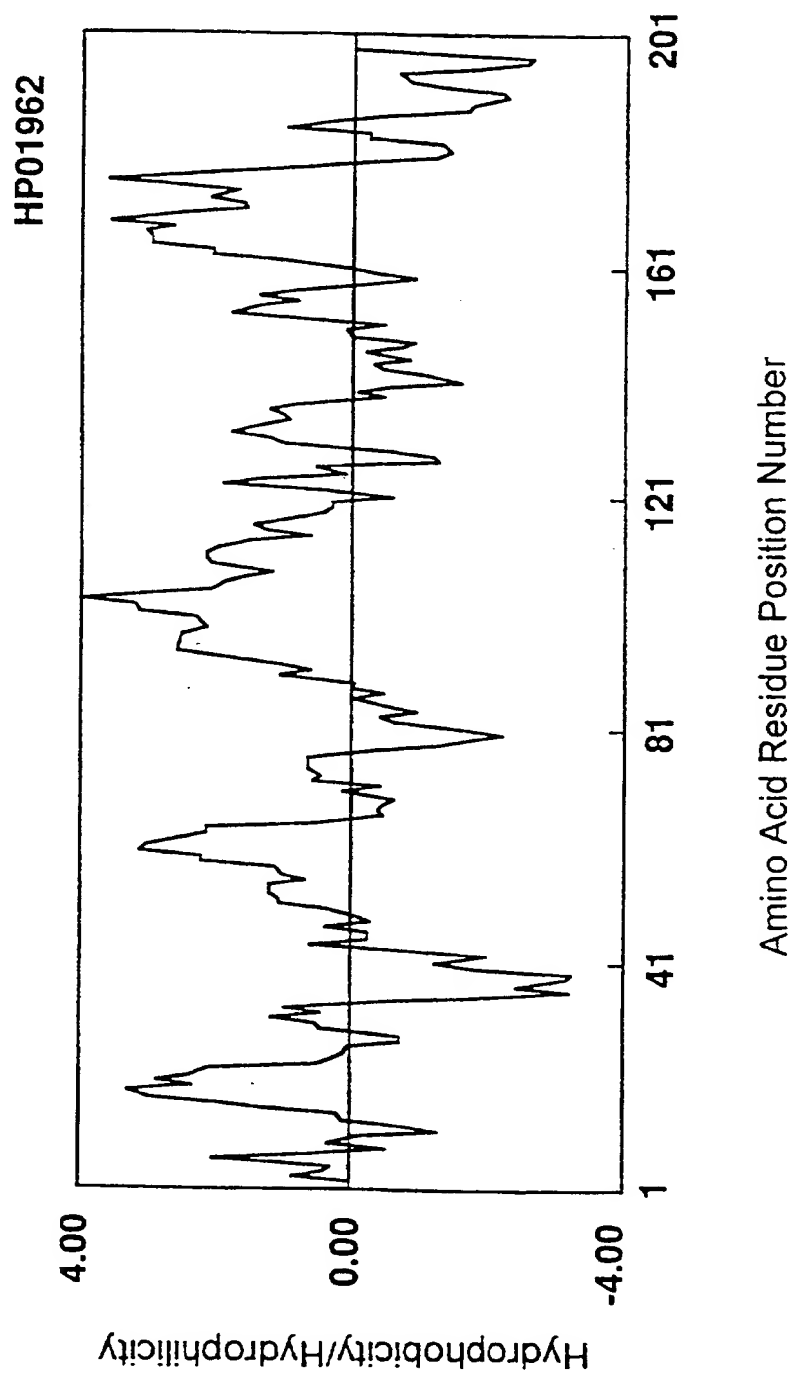


Fig. 6

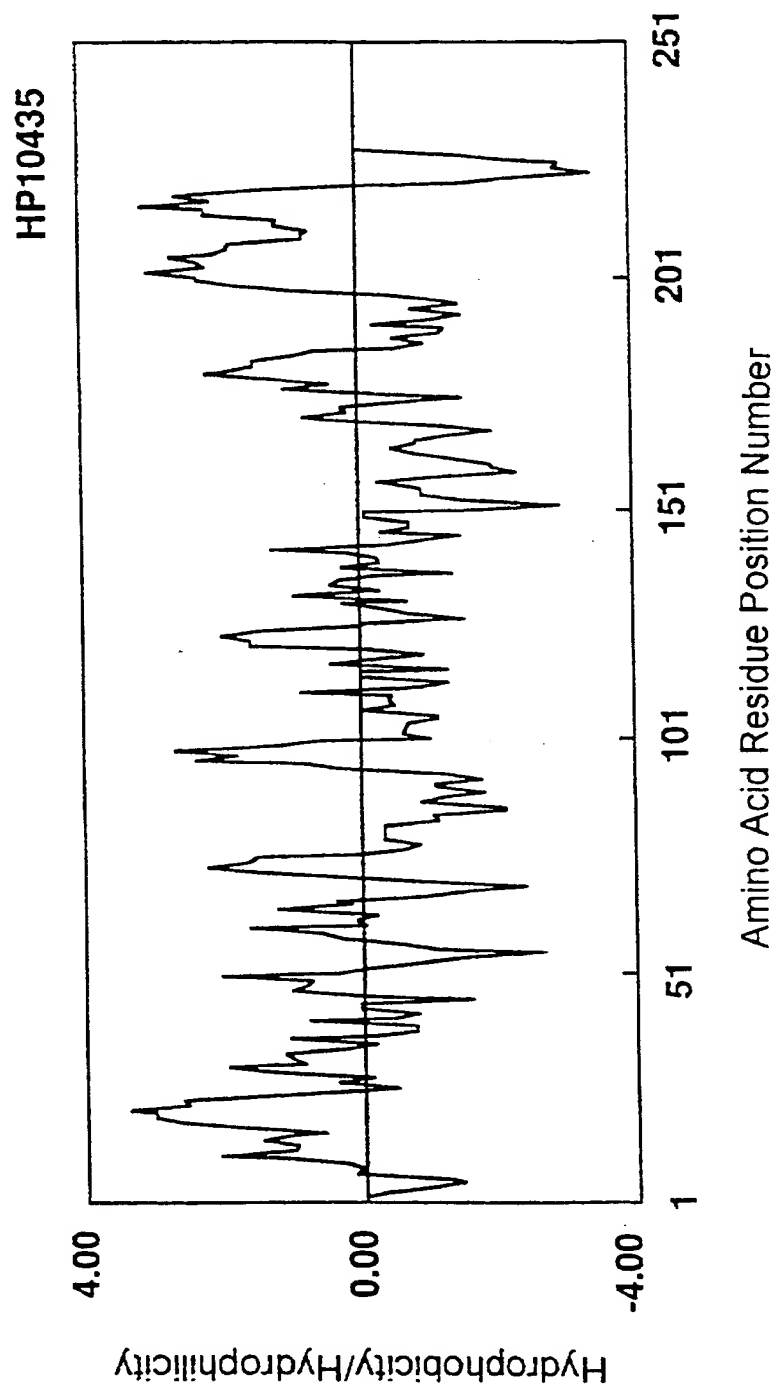


Fig. 7

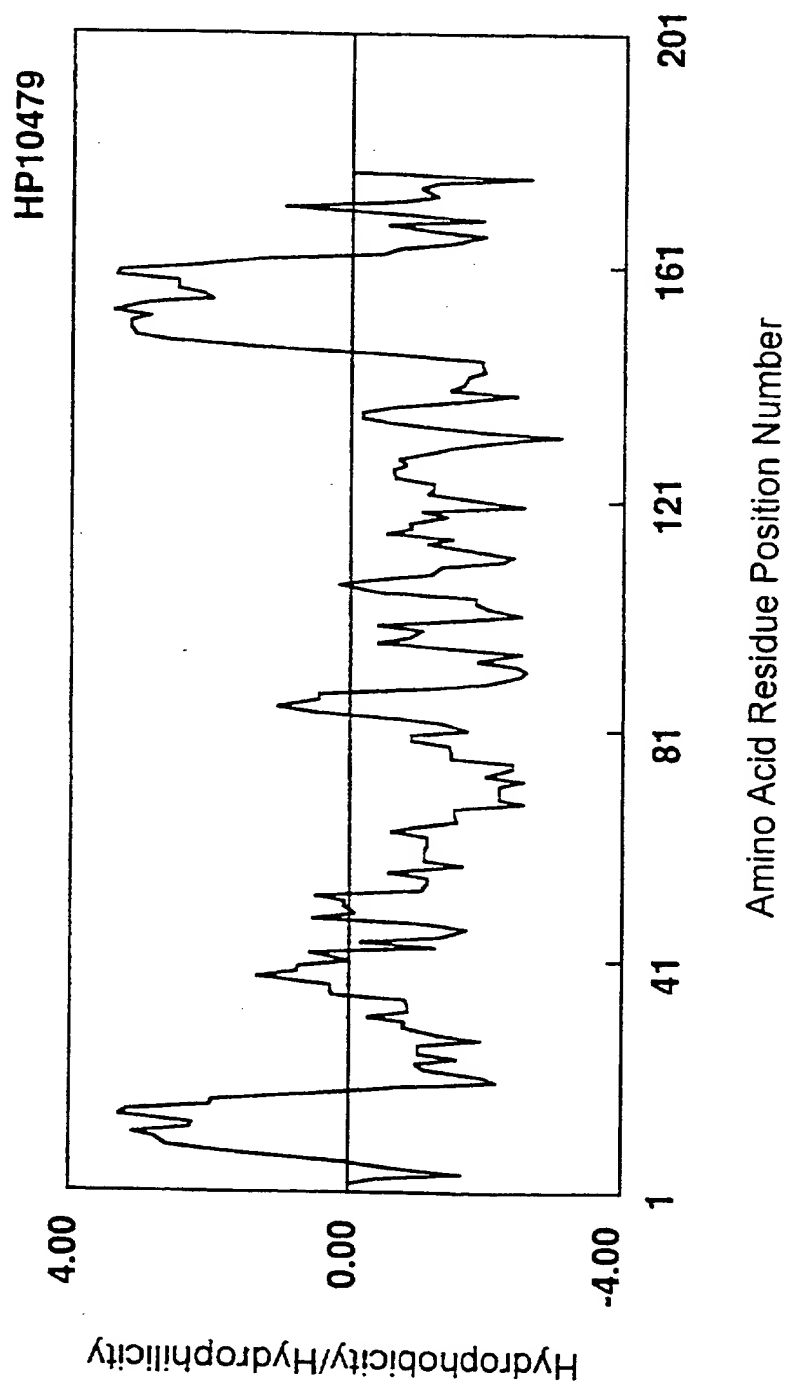


Fig. 8

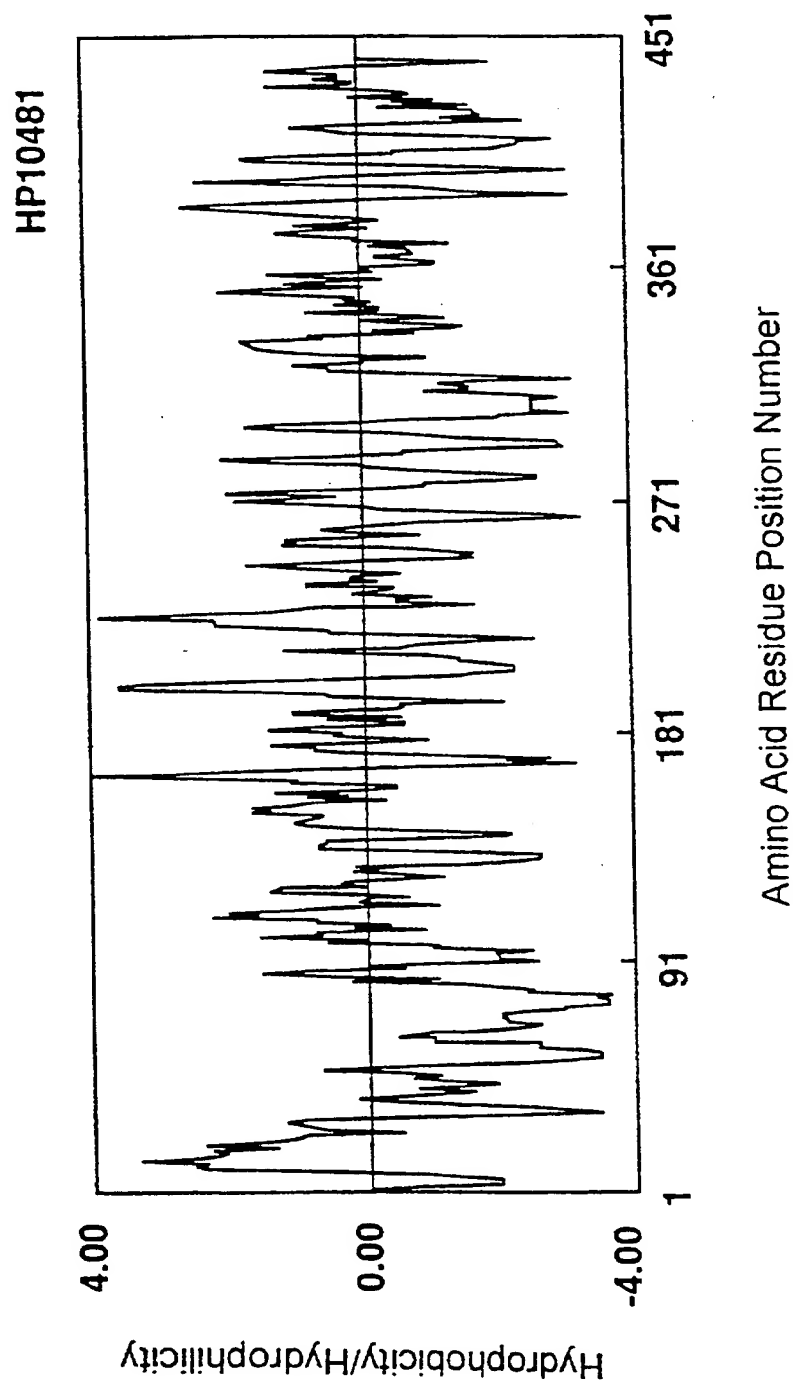


Fig. 9

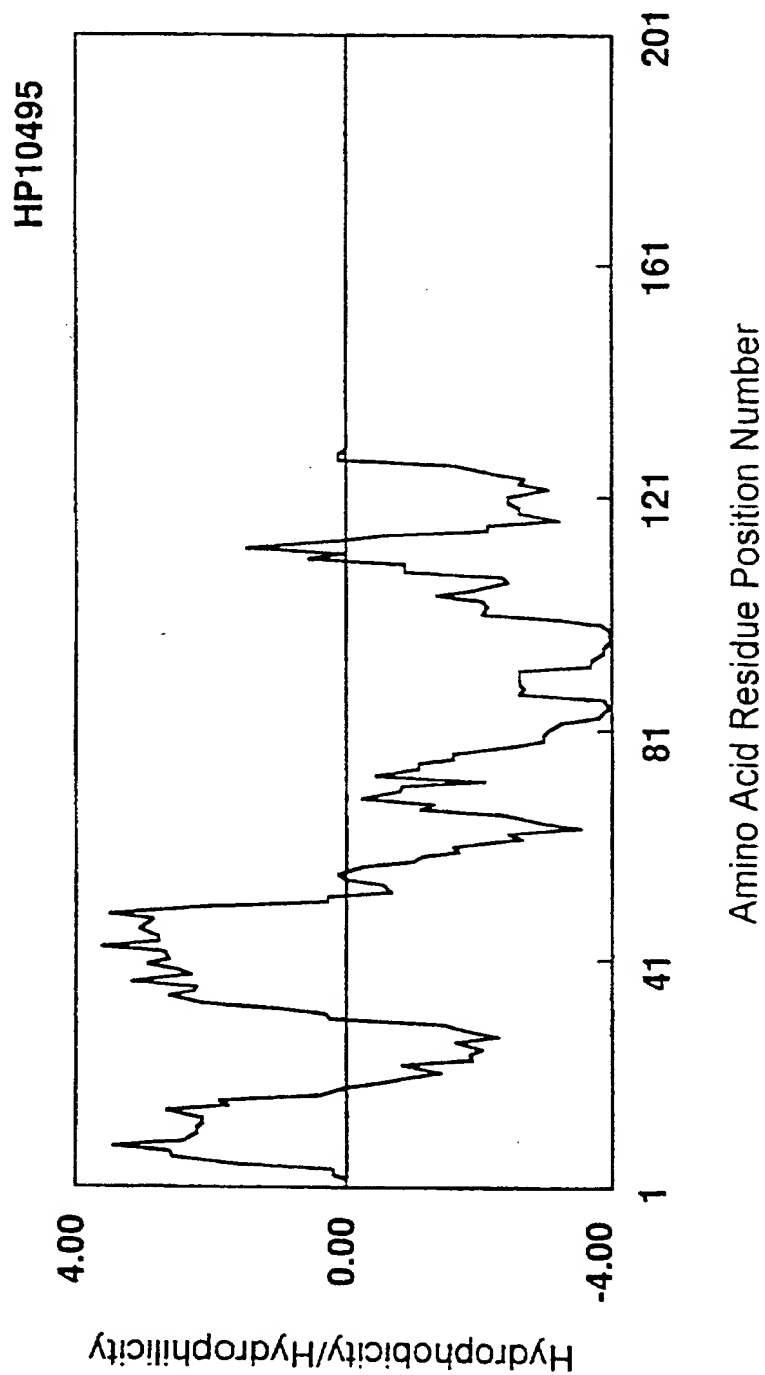


Fig. 10

Sequence Listing

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35

40

45

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50

55

60

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65

70

75

80

Lys Lys Asn Ile Thr Cys Cys Asp Thr Asp Leu Cys Asn Ala Ser Gly

85

90

95

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40

45

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Thr Gly Leu Leu Leu Thr Val Leu Val Ala Leu Thr Tyr Ile Val Ala

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Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser

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100

105

110

Pro Ser Thr Asp Val Gln Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly

115

120

125

Phe His Glu Asp Asp Pro Phe Phe Tyr Asp Glu His Thr Leu Arg Lys

130

135

140

25 Arg Gly Leu Leu Val Ala Ala Val Leu Phe Ile Thr Gly Ile Ile Ile

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175

Cys Arg

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<212> PRT

<213> Homo sapiens

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25

30

15 Arg Gln Ala Pro Ala Gly Ser Pro Arg Gly Leu Arg Lys Gly Ala Ala

35

40

45

Pro Ala Arg Glu Arg Arg Gly Arg Glu Gln Ser Thr Leu Glu Ser Glu

50

55

60

Glu Trp Asn Pro Trp Glu Gly Asp Glu Lys Asn Glu Gln Gln His Arg

20

65

70

75

80

Phe Lys Thr Ser Leu Gln Ile Leu Asp Lys Ser Thr Lys Gly Lys Thr

85

90

95

Asp Leu Ser Val Gln Ile Trp Gly Lys Ala Ala Ile Gly Leu Tyr Leu

100

105

110

25 Trp Glu His Ile Phe Glu Gly Leu Leu Asp Pro Ser Asp Val Thr Ala

115

120

125

Gln Trp Arg Glu Gly Lys Ser Ile Val Gly Arg Thr Gln Tyr Ser Phe

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	Leu Gln His Leu Ala Val Val Leu Leu Gly Asn Glu His Cys Asp Asn		
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	Leu Phe Ile Ile Tyr Asp Ser Pro Trp Ile Asn Asp Val Asp Val Phe		
	225	230	235 240
	Gln Trp Pro Leu Gly Val Ala Thr Tyr Arg Asn Phe Pro Val Val Glu		
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	Ala Ser Trp Ser Met Leu His Asp Glu Arg Pro Tyr Leu Cys Asn Phe		
	260	265	270
	Leu Gly Thr Ile Tyr Glu Asn Ser Ser Arg Gln Ala Leu Met Asn Ile		
	275	280	285
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	290	295	300
	His Trp Gln Pro Gln Glu Thr Asn Glu Ser Leu Lys Asn Tyr Gln Asp		
	305	310	315 320
	Ala Leu Leu Gln Ser Asp Leu Thr Leu Cys Pro Val Gly Val Asn Thr		
25	325	330	335
	Glu Cys Tyr Arg Ile Tyr Glu Ala Cys Ser Tyr Gly Ser Ile Pro Val		
	340	345	350

Val Glu Asp Val Met Thr Ala Gly Asn Cys Gly Asn Thr Ser Val His

355

360

365

His Gly Ala Pro Leu Gln Leu Leu Lys Ser Met Gly Ala Pro Phe Ile

370

375

380

5 Phe Ile Lys Asn Trp Lys Glu Leu Pro Ala Val Leu Glu Lys Glu Lys

385

390

395

400

Thr Ile Ile Leu Gln Glu Lys Ile Glu Arg Arg Lys Met Leu Leu Gln

405

410

415

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25

30

25 Val Gly Leu Ala Ala Val Val Gly Phe Leu Phe Ile Val Tyr Leu Val

35

40

45

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 5 85 90 95
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<212> DNA

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5 <213> Homo sapiens

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<211> 243

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gac

903

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<211> 534

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	Val Ile Ser Lys Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp	
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25	ctg ctc cct gca ctc ggc ctg ctg ctc tgg gga ccc ggc cag cta	384
	Leu Leu Pro Ala Leu Gly Leu Leu Leu Trp Gly Pro Gly Gln Leu	
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15

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Gln Val Ser Asn Glu Asp Cys Leu Gln Val Lys Asn Cys Thr Gln Leu

30

35

40

25

Gly Glu Gln Cys Trp Thr Ala Arg Ile Arg Ala Val Gly Leu Leu Thr

45

50

55

60

Val Ile Ser Lys Gly Cys Ser Leu Asn Cys Val Asp Asp Ser Gln Asp

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	Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser Ala Phe Ile		
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	Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly Gly Ala Leu	
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 180 185 190 195
 gtc gtc tac tcc gcg ccg cgc tcc acc gcc ccg gga gcc agc ctg gcc 860
 5 Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala Ser Leu Gly
 200 205 210
 aca gcc tac gac cgc aag gac tac gtc taa gggacagacg cagggagacc 910
 Thr Gly Tyr Asp Arg Lys Asp Tyr Val
 215 220
 10 ccaccaccac caccaccacc aacaccacca ccaccacagc gagctggagc gcgcaccagg 970
 ccatccagcg tgcagccttg cctcggaggc cagcccaccc ccagaagcca ggaagccccc 1030
 gcgctggact ggggcagctt ccccagcagc cagcgctttg cgggccgggc agtcgacttc 1090
 ggggcccagg gaccaacctg catggactgt gaaacctcac ctttctggag cacggggcct 1150
 ggggtgaccgc caatacttga ccaccccgtc gagccccatc ggcccgctgc ccccatgtc 1210
 15 gcgctgggca gggaccggca gccctggaag gggcacttga tatttttcaa taaaagcctt 1270
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20 <211> 220

<212> PRT

<213> Homo sapiens

<400> 24

25

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Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly Trp Leu Gly

NSDOCID: CWO 941R203A2 1 5

<210> 25

<211> 835

5 <212> DNA

<213> Homo sapiens

<400> 25

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Met Ala Tyr His Gly Leu Thr Val Pro Leu Ile Val Met Ser Val
1 5 10 15
ttc tgg ggc ttc gtc ggc ttc ttg gtg cct tgg ttc atc cct aag ggt 155
Phe Trp Gly Phe Val Gly Phe Leu Val Pro Trp Phe Ile Pro Lys Gly
15 20 25 30
cct aac cgg gga gtt atc att acc atg ttg gtg acc tgt tca gtt tgc 203
Pro Asn Arg Gly Val Ile Ile Thr Met Leu Val Thr Cys Ser Val Cys
35 40 45
tgc tat ctc ttt tgg ctg att gca att ctg gcc caa ctc aac cct ctc 251
20 Cys Tyr Leu Phe Trp Leu Ile Ala Ile Leu Ala Gln Leu Asn Pro Leu
50 55 60
ttt gga ccg caa ttg aaa aat gaa acc atc tgg tat ctg aag tat cat 299
Phe Gly Pro Gln Leu Lys Asn Glu Thr Ile Trp Tyr Leu Lys Tyr His
65 70 75
25 tgg cct tgagg aagaagacat gctctacagt gctcagtcctt tgaggtcacg 350
Trp Pro
80

agaagagaat gccttctaga tgcaaaatca cctccaaacc agaccacttt tcttgacttg 410
 cctgttttgg ccattagctg ccttaaactg taacagcaca ttigaatgcc ttattctaca 470
 atgcagegtg ttttctttg ccttttttgc acttttggtga attacgtgcc tccataacct 530
 gaactgtgcc gactccacaa aacgattatg tactcttctg agatagaaga tgctgttctt 590
 5 ctgagagata cgttactctc tcttggaaat ctgtggattt gaagatggct cctgccttct 650
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 tggtcagtag gagagcacgt tcagagggaa gagccatctc aacagaatcg caccaaacta 770
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 tatgg 835

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<210> 26

<211> 81

<212> PRT

15 <213> Homo sapiens

<400> 26

Met Ala Tyr His Gly Leu Thr Val Pro Leu Ile Val Met Ser Val

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20 Phe Trp Gly Phe Val Gly Phe Leu Val Pro Trp Phe Ile Pro Lys Gly

20	25	30
----	----	----

Pro Asn Arg Gly Val Ile Ile Thr Met Leu Val Thr Cys Ser Val Cys

35	40	45
----	----	----

Cys Tyr Leu Phe Trp Leu Ile Ala Ile Leu Ala Gln Leu Asn Pro Leu

25	50	55	60
----	----	----	----

Phe Gly Pro Gln Leu Lys Asn Glu Thr Ile Trp Tyr Leu Lys Tyr His

65	70	75
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Trp Pro

80

5 <210> 27

<211> 1256

<212> DNA

<213> Homo sapiens

10 <400> 27

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ggcc atg cta gcc ttg cgc gtg gcg cgc ggc tgc tgg ggg gcc ctg cgc 169

Met Leu Ala Leu Arg Val Ala Arg Gly Ser Trp Gly Ala Leu Arg

15 1 5 10 15

ggc gcc gct tgg gct ccg gga acg cgg ccg agt aag cga cgc gcc tgc 217

Gly Ala Ala Trp Ala Pro Gly Thr Arg Pro Ser Lys Arg Arg Ala Cys

20 25 30

tgg gcc ctg ctg ccg ccc gtg ccc tgc tgc ttg ggc tgc ctg gcc gaa 265

20 Trp Ala Leu Leu Pro Pro Val Pro Cys Cys Leu Gly Cys Leu Ala Glu

35 40 45

cgc tgg agg ctg cgt ccg gcc gct ctt ggc ttg cgg ctg ccc ggg atc 313

Arg Trp Arg Leu Arg Pro Ala Ala Leu Gly Leu Arg Leu Pro Gly Ile

50 55 60

25 ggc cag cgg aac cac tgt tgc ggc gcg ggg aag gcg gct ccc agg cca 361

Gly Gln Arg Asn His Cys Ser Gly Ala Gly Lys Ala Ala Pro Arg Pro

65 70 75

gcg gcc gga gcg ggc gcc gct gcc gaa gcc ccg ggc ggc cag tgg ggc 409
 Ala Ala Gly Ala Gly Ala Ala Ala Glu Ala Pro Gly Gly Gln Trp Gly
 80 85 90 95
 ccg gcg agc acc ccc agc ctg tat gaa aac cca tgg aca atc ccg aat 457
 5 Pro Ala Ser Thr Pro Ser Leu Tyr Glu Asn Pro Trp Thr Ile Pro Asn
 100 105 110
 atg ttg tca atg acg aga att ggc ttg gcc cca gtt ctg ggc tat ttg 505
 Met Leu Ser Met Thr Arg Ile Gly Leu Ala Pro Val Leu Gly Tyr Leu
 115 120 125
 10 att att gaa gaa gat ttt aat att gca cta gga gtt ttt gct tta gct 553
 Ile Ile Glu Glu Asp Phe Asn Ile Ala Leu Gly Val Phe Ala Leu Ala
 130 135 140
 gga cta aca gat ttg ttg gat gga ttt att gct cga aac tgg gcc aat 601
 Gly Leu Thr Asp Leu Leu Asp Gly Phe Ile Ala Arg Asn Trp Ala Asn
 15 145 150 155
 caa aga tca gct ttg gga agt gct ctt gat cca ctt gct gat aaa ata 649
 Gln Arg Ser Ala Leu Gly Ser Ala Leu Asp Pro Leu Ala Asp Lys Ile
 160 165 170 175
 ctt atc agt atc tta tat gtt agc ttg acc tat gca gat ctt att cca 697
 20 Leu Ile Ser Ile Leu Tyr Val Ser Leu Thr Tyr Ala Asp Leu Ile Pro
 180 185 190
 gtt cca ctt act tac atg atc att tcg aga gat gta atg ttg att gct 745
 Val Pro Leu Thr Tyr Met Ile Ile Ser Arg Asp Val Met Leu Ile Ala
 195 200 205
 25 gct gtt ttt tat gtc aga tac cga act ctt cca aca cca cga aca ctt 793
 Ala Val Phe Tyr Val Arg Tyr Arg Thr Leu Pro Thr Pro Arg Thr Leu
 210 215 220

gcc aag tat ttc aat cct tgc tat gcc act gct agg tta aaa cca aca 841
Ala Lys Tyr Phe Asn Pro Cys Tyr Ala Thr Ala Arg Leu Lys Pro Thr
225 230 235
ttc atc agc aag gtg aat aca gca gtc cag tta atc ttg gtg gca gct 889
5 Phe Ile Ser Lys Val Asn Thr Ala Val Gln Leu Ile Leu Val Ala Ala
240 245 250 255
tct ttg gca gct cca gtt ttc aac tat gct gac agc att tat ctt cag 937
Ser Leu Ala Ala Pro Val Phe Asn Tyr Ala Asp Ser Ile Tyr Leu Gln
260 265 270
10 ata cta tgg tgt ttt aca gct ttc acc aca gct gca tca gct tat agt 985
Ile Leu Trp Cys Phe Thr Ala Phe Thr Thr Ala Ala Ser Ala Tyr Ser
275 280 285
tac tat cat tat ggc cgg aag act gtt cag gtg ata aaa gac tga 1030
Tyr Tyr His Tyr Gly Arg Lys Thr Val Gln Val Ile Lys Asp
15 290 295 300
tgaaagtcac cctcactgt tagtaaggaa gcagtataca tcaatgggaa cagggcccat 1090
ggaaatgtac aggagtttcc ctattttggt gttcagcttg aaaaaggact tgcagaatc 1150
aactgtgtca tcaaaattta agtaatgtgc attgaaaata aggttgatca tgggaatatg 1210
cagaatttcc aatgtatttt taaatacaaa taaaattgta atttag 1256
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<210> 28

<211> 301

<212> PRT
25 <213> Homo sapiens

<400> 28

Met Leu Ala Leu Arg Val Ala Arg Gly Ser Trp Gly Ala Leu Arg
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20 25 30
5 Trp Ala Leu Leu Pro Pro Val Pro Cys Cys Leu Gly Cys Leu Ala Glu
35 40 45
Arg Trp Arg Leu Arg Pro Ala Ala Leu Gly Leu Arg Leu Pro Gly Ile
50 55 60
Gly Gln Arg Asn His Cys Ser Gly Ala Gly Lys Ala Ala Pro Arg Pro
10 65 70 75
Ala Ala Gly Ala Gly Ala Ala Ala Glu Ala Pro Gly Gly Gln Trp Gly
80 85 90 95
Pro Ala Ser Thr Pro Ser Leu Tyr Glu Asn Pro Trp Thr Ile Pro Asn
100 105 110
15 Met Leu Ser Met Thr Arg Ile Gly Leu Ala Pro Val Leu Gly Tyr Leu
115 120 125
Ile Ile Glu Glu Asp Phe Asn Ile Ala Leu Gly Val Phe Ala Leu Ala
130 135 140
Gly Leu Thr Asp Leu Leu Asp Gly Phe Ile Ala Arg Asn Trp Ala Asn
20 145 150 155
Gln Arg Ser Ala Leu Gly Ser Ala Leu Asp Pro Leu Ala Asp Lys Ile
160 165 170 175
Leu Ile Ser Ile Leu Tyr Val Ser Leu Thr Tyr Ala Asp Leu Ile Pro
180 185 190
25 Val Pro Leu Thr Tyr Met Ile Ile Ser Arg Asp Val Met Leu Ile Ala
195 200 205
Ala Val Phe Tyr Val Arg Tyr Arg Thr Leu Pro Thr Pro Arg Thr Leu

	30	35	40	
	ctg tcc gag ctg cag tat tac ctc acc acg gag gtg cat cct gag ctc			195
	Leu Ser Glu Leu Gln Tyr Tyr Leu Thr Thr Glu Val His Pro Glu Leu			
	45	50	55	
5	tac gtg gac aag tgc cgg gga gat aaa ctg aag atc aac atc gat gta			243
	Tyr Val Asp Lys Ser Arg Gly Asp Lys Leu Lys Ile Asn Ile Asp Val			
	60	65	70	
	ctt ttt ccg cac atg cct tgt gcc tat ctg agt att gat gcc atg gat			291
	Leu Phe Pro His Met Pro Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp			
10	75	80	85	90
	gtg gcc gga gaa cag cag ctg gat gtg gaa cac aac ctg ttc aag caa			339
	Val Ala Gly Glu Gln Gln Leu Asp Val Glu His Asn Leu Phe Lys Gln			
	95	100	105	
	cga cta gat aaa gat ggc atc ccc gtg agc tca gag gct gag cgg cat			387
15	Arg Leu Asp Lys Asp Gly Ile Pro Val Ser Ser Glu Ala Glu Arg His			
	110	115	120	
	gag ctt ggg aaa gtc gag gtg acg gtg ttt gac cct gac tcc ctg gac			435
	Glu Leu Gly Lys Val Glu Val Thr Val Phe Asp Pro Asp Ser Leu Asp			
	125	130	135	
20	cct gat cgc tgt gag agc tgc tat ggt gct gag gca gaa gat atc aag			483
	Pro Asp Arg Cys Glu Ser Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys			
	140	145	150	
	tgc tgt aac acc tgt gaa gat gtg cgg gag gca tat cgc cgt aga ggc			531
	Cys Cys Asn Thr Cys Glu Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly			
25	155	160	165	170
	tgg gcc ttc aag aac cca gat act att gag cag tgc cgg cga gag ggc			579
	Trp Ala Phe Lys Asn Pro Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly			

	175	180	185	
	ttc agc cag aag atg cag gag cag aag aat gaa ggc tgc cag gtg tat			627
	Phe Ser Gln Lys Met Gln Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr			
	190	195	200	
5	ggc ttc ttg gaa gtc aat aag gtg gcc gga aac ttc cac ttt gcc cct			675
	Gly Phe Leu Glu Val Asn Lys Val Ala Gly Asn Phe His Phe Ala Pro			
	205	210	215	
	ggg aag agc ttc cag cag tcc cat gtg cac gtc cat gac ttg cag agc			723
	Gly Lys Ser Phe Gln Gln Ser His Val His Val His Asp Leu Gln Ser			
10	220	225	230	
	ttt ggc ctt gac aac atc aac atg acc cac tac atc cag cac ctg tca			771
	Phe Gly Leu Asp Asn Ile Asn Met Thr His Tyr Ile Gln His Leu Ser			
	235	240	245	250
	ttt ggg gag gac tat cca ggc att gtg aac ccc ctg gac cac acc aat			819
15	Phe Gly Glu Asp Tyr Pro Gly Ile Val Asn Pro Leu Asp His Thr Asn			
	255	260	265	
	gtc act gcg ccc caa gcc tcc atg atg ttc cag tac ttt gtg aag gtg			867
	Val Thr Ala Pro Gln Ala Ser Met Met Phe Gln Tyr Phe Val Lys Val			
	270	275	280	
20	gtg ccc act gtg tac atg aag gtg gac gga gag gta ctg agg aca aat			915
	Val Pro Thr Val Tyr Met Lys Val Asp Gly Glu Val Leu Arg Thr Asn			
	285	290	295	
	cag ttc tct gtg acc aga cat gag aag gtt gcc aat ggg ctg ttg ggc			963
	Gln Phe Ser Val Thr Arg His Glu Lys Val Ala Asn Gly Leu Leu Gly			
25	300	305	310	
	gac caa ggc ctt ccc gga gtc ttc gtc ctc tat gag ctc tcg ccc atg			1011
	Asp Gln Gly Leu Pro Gly Val Phe Val Leu Tyr Glu Leu Ser Pro Met			

315 320 325 330
 atg gtg aag ctg acg gag aag cac agg tcc ttc acc cac ttc ctg aca 1059
 Met Val Lys Leu Thr Glu Lys His Arg Ser Phe Thr His Phe Leu Thr
 335 340 345
 5 ggt gtg tgc gcc atc att ggg ggc atg ttc aca gtg gct gga ctc atc 1107
 Gly Val Cys Ala Ile Ile Gly Gly Met Phe Thr Val Ala Gly Leu Ile
 350 355 360
 gat tgc ctc atc tac cac tca gca cga gcc atc cag aag aaa att gat 1155
 Asp Ser Leu Ile Tyr His Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp
 10 365 370 375
 cta ggg aag aca acg tagtcaccct cgggtgcttcc tctgtctcct ctttctccct 1210
 Leu Gly Lys Thr Thr
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<210> 30

<211> 383

20 <212> PRT

<213> Homo sapiens

<400> 30

Met Glu Ala Leu Gly Lys Leu Lys Gln Phe

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Asp Ala Tyr Pro Lys Thr Leu Glu Asp Phe Arg Val Lys Thr Cys Gly

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20

25

Gly Ala Thr Val Thr Ile Val Ser Gly Leu Leu Met Leu Leu Leu Phe
30 35 40
Leu Ser Glu Leu Gln Tyr Tyr Leu Thr Thr Glu Val His Pro Glu Leu
45 50 55
5 Tyr Val Asp Lys Ser Arg Gly Asp Lys Leu Lys Ile Asn Ile Asp Val
60 65 70
Leu Phe Pro His Met Pro Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp
75 80 85 90
Val Ala Gly Glu Gln Gln Leu Asp Val Glu His Asn Leu Phe Lys Gln
10 95 100 105
Arg Leu Asp Lys Asp Gly Ile Pro Val Ser Ser Glu Ala Glu Arg His
110 115 120
Glu Leu Gly Lys Val Glu Val Thr Val Phe Asp Pro Asp Ser Leu Asp
125 130 135
15 Pro Asp Arg Cys Glu Ser Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys
140 145 150
Cys Cys Asn Thr Cys Glu Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly
155 160 165 170
Trp Ala Phe Lys Asn Pro Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly
20 175 180 185
Phe Ser Gln Lys Met Gln Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr
190 195 200
Gly Phe Leu Glu Val Asn Lys Val Ala Gly Asn Phe His Phe Ala Pro
205 210 215
25 Gly Lys Ser Phe Gln Gln Ser His Val His Val His Asp Leu Gln Ser
220 225 230
Phe Gly Leu Asp Asn Ile Asn Met Thr His Tyr Ile Gln His Leu Ser

235 240 245 250
Phe Gly Glu Asp Tyr Pro Gly Ile Val Asn Pro Leu Asp His Thr Asn
 255 260 265
Val Thr Ala Pro Gln Ala Ser Met Met Phe Gln Tyr Phe Val Lys Val
5 270 275 280
Val Pro Thr Val Tyr Met Lys Val Asp Gly Glu Val Leu Arg Thr Asn
 285 290 295
Gln Phe Ser Val Thr Arg His Glu Lys Val Ala Asn Gly Leu Leu Gly
 300 305 310
10 Asp Gln Gly Leu Pro Gly Val Phe Val Leu Tyr Glu Leu Ser Pro Met
315 320 325 330
Met Val Lys Leu Thr Glu Lys His Arg Ser Phe Thr His Phe Leu Thr
 335 340 345
Gly Val Cys Ala Ile Ile Gly Gly Met Phe Thr Val Ala Gly Leu Ile
15 350 355 360
Asp Ser Leu Ile Tyr His Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp
 365 370 375
Leu Gly Lys Thr Thr
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20

<210> 31

<211> 899

<212> DNA

25 <213> Homo sapiens

<400> 31

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 Met Thr Arg Leu Leu Gly Tyr Val Asp Pro Leu Asp
 1 5 10
 5 ccc age ttt gtg gct gcc gtc atc acc atc acc ttc aat ccg ctc tac 157
 Pro Ser Phe Val Ala Ala Val Ile Thr Ile Thr Phe Asn Pro Leu Tyr
 15 20 25
 tgg aat gtg gtt gca cga tgg gaa cac aag acc cgc aag ctg agc agg 205
 Trp Asn Val Val Ala Arg Trp Glu His Lys Thr Arg Lys Leu Ser Arg
 10 30 35 40
 gcc ttc gga tcc ccc tac ctg gcc tgc tac tct cta agc gtc acc atc 253
 Ala Phe Gly Ser Pro Tyr Leu Ala Cys Tyr Ser Leu Ser Val Thr Ile
 45 50 55 60
 ctg ctc ctg aac ttc ctg cgc tgc cac tgc ttc acg cag gcc atg ctg 301
 15 Leu Leu Leu Asn Phe Leu Arg Ser His Cys Phe Thr Gln Ala Met Leu
 65 70 75
 agc cag ccc agg atg gag agc ctg gac acc ccc gcg gcc tac agc ctg 349
 Ser Gln Pro Arg Met Glu Ser Leu Asp Thr Pro Ala Ala Tyr Ser Leu
 80 85 90
 20 ggc ctc gcg ctc ctg gga ctg ggc gtc gtg ctc gtg ctc tcc agc ttc 397
 Gly Leu Ala Leu Leu Gly Leu Gly Val Val Leu Val Leu Ser Ser Phe
 95 100 105
 ttt gca ctg ggg ttc gct gga act ttc cta ggt gat tac ttc ggg atc 445
 Phe Ala Leu Gly Phe Ala Gly Thr Phe Leu Gly Asp Tyr Phe Gly Ile
 25 110 115 120
 ctc aag gag gcg aga gtg acc gtg ttc ccc ttc aac atc ctg gac aac 493
 Leu Lys Glu Ala Arg Val Thr Val Phe Pro Phe Asn Ile Leu Asp Asn

125 130 135 140
 ccc atg tac tgg gga agc aca gcc aac tac ctg ggc tgg gcc atc atg 541
 Pro Met Tyr Trp Gly Ser Thr Ala Asn Tyr Leu Gly Trp Ala Ile Met
 145 150 155
 5 cac gcc agc ccc acg ggc ctg ctc ctg acg gtg ctg gtg gcc ctc acc 589
 His Ala Ser Pro Thr Gly Leu Leu Leu Thr Val Leu Val Ala Leu Thr
 160 165 170
 tac ata gtg gct ctc cta tac gaa gag ccc ttc acc gct gag atc tac 637
 Tyr Ile Val Ala Leu Leu Tyr Glu Glu Pro Phe Thr Ala Glu Ile Tyr
 10 175 180 185
 cgg cag aaa gcc tcc ggg tcc cac aag agg agc tgattgagct gcaacagctt 690
 Arg Gln Lys Ala Ser Gly Ser His Lys Arg Ser
 190 195
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 15 aatggtgcct gctgctcagg gctcgcccc ggctgtgggt gccccagtgc cttggaacct 810
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20 <210> 32
 <211> 199
 <212> PRT
 <213> Homo sapiens

25 <400> 32

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15 20 25

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30 35 40

5 Ala Phe Gly Ser Pro Tyr Leu Ala Cys Tyr Ser Leu Ser Val Thr Ile
45 50 55 60

Leu Leu Leu Asn Phe Leu Arg Ser His Cys Phe Thr Gln Ala Met Leu
65 70 75

Ser Gln Pro Arg Met Glu Ser Leu Asp Thr Pro Ala Ala Tyr Ser Leu
10 80 85 90

Gly Leu Ala Leu Leu Gly Leu Gly Val Val Leu Val Leu Ser Ser Phe
95 100 105

Phe Ala Leu Gly Phe Ala Gly Thr Phe Leu Gly Asp Tyr Phe Gly Ile
110 115 120

15 Leu Lys Glu Ala Arg Val Thr Val Phe Pro Phe Asn Ile Leu Asp Asn
125 130 135 140

Pro Met Tyr Trp Gly Ser Thr Ala Asn Tyr Leu Gly Trp Ala Ile Met
145 150 155

His Ala Ser Pro Thr Gly Leu Leu Leu Thr Val Leu Val Ala Leu Thr
20 160 165 170

Tyr Ile Val Ala Leu Leu Tyr Glu Glu Pro Phe Thr Ala Glu Ile Tyr
175 180 185

Arg Gln Lys Ala Ser Gly Ser His Lys Arg Ser
190 195

25

<210> 33

<211> 905

<212> DNA

<213> Homo sapiens

5 <400> 33

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Met Ala Pro His Gly Pro Gly Ser Leu Thr Thr Leu Val Pro

1

5

10

tgg gct gcc gcc ctg ctc ctc gct ctg ggc gtg gaa agg gct ctg gcg 98

10 Trp Ala Ala Ala Leu Leu Leu Ala Leu Gly Val Glu Arg Ala Leu Ala

15

20

25

30

cta ccc gag ata tgc acc caa tgt cca ggg agc gtg caa aat ttg tca 146

Leu Pro Glu Ile Cys Thr Gln Cys Pro Gly Ser Val Gln Asn Leu Ser

35

40

45

15 aaa gtg gcc ttt tat tgt aaa acg aca cga gag cta atg ctg cat gcc 194

Lys Val Ala Phe Tyr Cys Lys Thr Thr Arg Glu Leu Met Leu His Ala

50

55

60

cgt tgc tgc ctg aat cag aag ggc acc atc ttg ggg ctg gat ctc cag 242

Arg Cys Cys Leu Asn Gln Lys Gly Thr Ile Leu Gly Leu Asp Leu Gln

20

65

70

75

aac tgt tct ctg gag gac cct ggt cca aac ttt cat cag gca cat acc 290

Asn Cys Ser Leu Glu Asp Pro Gly Pro Asn Phe His Gln Ala His Thr

80

85

90

act gtc atc ata gac ctg caa gca aac ccc ctc aaa ggt gac ttg gcc 338

25 Thr Val Ile Ile Asp Leu Gln Ala Asn Pro Leu Lys Gly Asp Leu Ala

95

100

105

110

aac acc ttc cgt ggc ttt act cag ctc cag act ctg ata ctg cca caa 386

Asn Thr Phe Arg Gly Phe Thr Gln Leu Gln Thr Leu Ile Leu Pro Gln
 115 120 125
 cat gtc aac tgt cct gga gga att aat gcc tgg aat act atc acc tct 434
 His Val Asn Cys Pro Gly Gly Ile Asn Ala Trp Asn Thr Ile Thr Ser
 5 130 135 140
 tat ata gac aac caa atc tgt caa ggg caa aag aac ctt tgc aat aac 482
 Tyr Ile Asp Asn Gln Ile Cys Gln Gly Gln Lys Asn Leu Cys Asn Asn
 145 150 155
 act ggg gac cca gaa atg tgt cct gag aat gga tct tgt gta cct gat 530
 10 Thr Gly Asp Pro Glu Met Cys Pro Glu Asn Gly Ser Cys Val Pro Asp
 160 165 170
 ggt cca ggt ctt ttg cag tgt gtt tgt gct gat ggt ttc cat gga tac 578
 Gly Pro Gly Leu Leu Gln Cys Val Cys Ala Asp Gly Phe His Gly Tyr
 175 180 185 190
 15 aag tgt atg cgc cag ggc tgg ttc tca ctg ctt atg ttc ttc ggg att 626
 Lys Cys Met Arg Gln Gly Ser Phe Ser Leu Leu Met Phe Phe Gly Ile
 195 200 205
 ctg gga gcc acc act cta tcc gtc tcc att ctg ctt tgg gcg acc cag 674
 Leu Gly Ala Thr Thr Leu Ser Val Ser Ile Leu Leu Trp Ala Thr Gln
 20 210 215 220
 cgc cga aaa gcc aag act tca tgaac tacataggtc ttaccattga 720
 Arg Arg Lys Ala Lys Thr Ser
 225
 cctaagatca atctgaacta tcttagccca gtcagggagc tctgcttccct agaaaggcat 780
 25 ctttcgccag tggattcgcc tcaaggttga ggccgccatt ggaagatgaa aaattgcact 840
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 ctttt 905

<210> 34

<211> 229

5 <212> PRT

<213> Homo sapiens

<400> 34

Met Ala Pro His Gly Pro Gly Ser Leu Thr Thr Leu Val Pro

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	Ala	Leu	Leu
	Leu	Ala	Leu
	Gly	Val	Glu
	Arg	Ala	Leu
	Ala		
	15	20	25
	30		
	Leu	Pro	Glu
	Ile	Cys	Thr
	Gln	Cys	Pro
	Gly	Ser	Val
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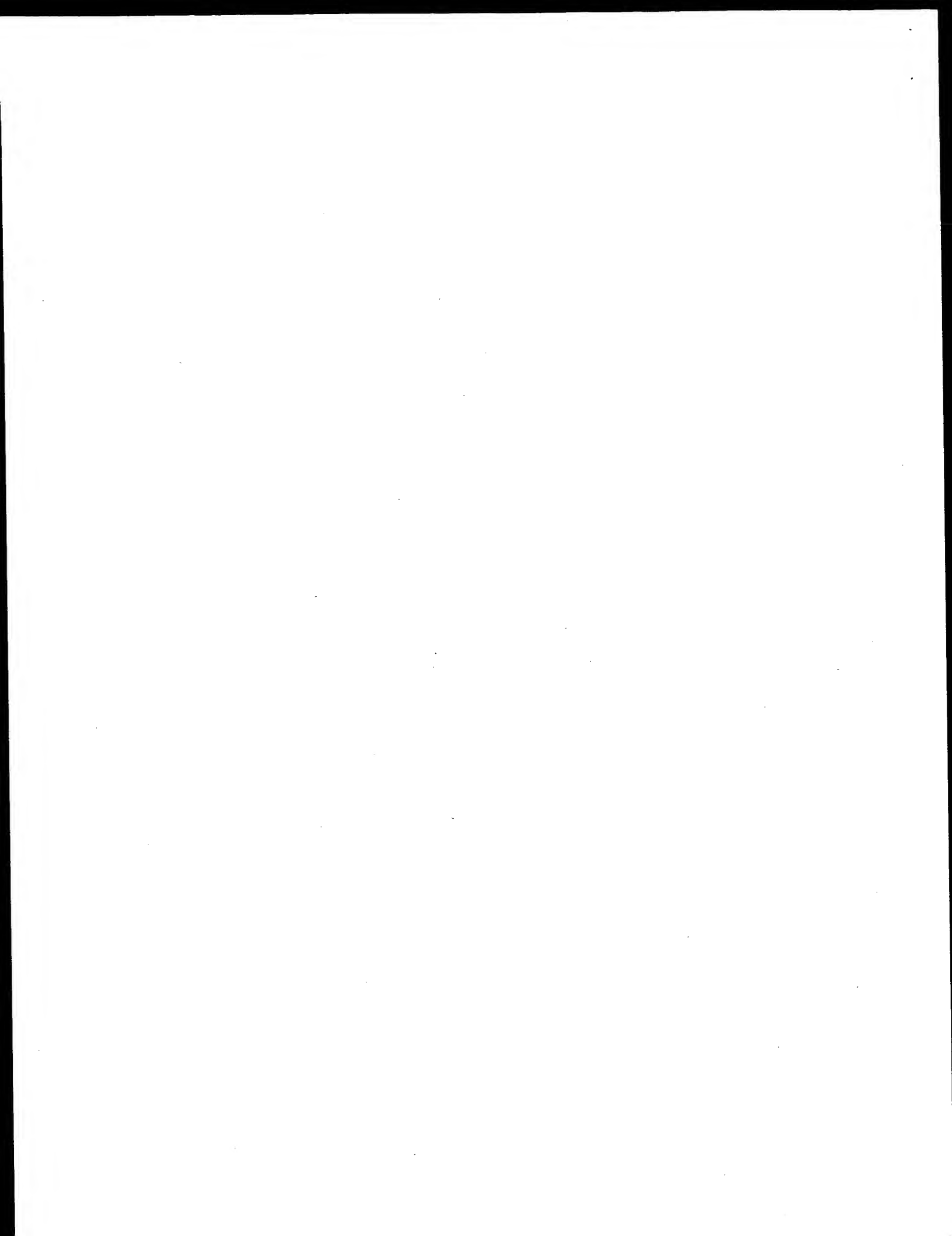
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/JP98/04475 (22) International Filing Date: 5 October 1998 (05.10.98) (30) Priority Data: 9/276271 8 October 1997 (08.10.97) JP (71) Applicants (for all designated States except US): SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho, Meguro-ku, Tokyo 153-0065 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP). YAMAGUCHI, Tomoko [JP/JP]; 5-13-11, Takasago, Katsushika-ku, Tokyo 125-0054 (JP). SEKINE, Shingo [JP/JP]; Remonzu 101, 2-8-15, Atago, Ageo-shi, Saitama 362-0034 (JP). KOBAYASHI, Midori [JP/JP]; Royal Court 306, 3-2-3, Minami-Rinkan, Yamato-shi, Kanagawa 242-0006 (JP). (74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).		(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of publication of the international search report: 24 June 1999 (24.06.99)
(54) Title: HUMAN PROTEINS HAVING TRANSMEMBRANE DOMAINS AND cDNAs ENCODING THESE PROTEINS		
(57) Abstract <p>The invention provides human proteins having transmembrane domains and cDNAs coding for these proteins as well as eukaryotic cells expressing said cDNAs. All of the proteins exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins can be employed as pharmaceuticals such as carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against said proteins. The cDNAs can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized for large-scale expression of said proteins. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening of novel low-molecular pharmaceuticals, and so on.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/04475

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 C12N15/79 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Genbank Database Entry GGSCA2A Accession number L34554; 16 July 1994 PETRENKO O. ET AL.: "Characterization of changes in gene expression associated with leukemic transformation by the NK-kB family member v-Rel" XP002089382 cited in the application see the whole document	1-6
A	EMBL Database Entry HS1268023 Accession number AA476643; 23 June 1997 HILLIER ET AL.: "WashU-Merck EST Project 1997" XP002089383 cited in the application see the whole document	1-6

-/-

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- *&* document member of the same patent family

Date of the actual completion of the international search

7 January 1999

Date of mailing of the international search report

23 04 99

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

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MONTERO LOPEZ B.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/04475

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 00540 A (INCYTE PHARMACEUTICALS, INC.) 8 January 1998 see page 2, line 18 - page 3, line 5 see sequences SEQ ID NO:2 and 4 ---	1-3,5,6
P,X	ROBERT E. REITER ET AL.: "Prostate stem cell antigen: A cell surface marker overexpressed in prostate cancer" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, no. 4, 17 February 1998, pages 1735-1740, XP002089381 WASHINGTON US see page 1735, right-hand column, paragraph 2; figure 2 ---	1,2,5,6
E	WO 98 51805 A (ABBOTT LABORATORIES) 19 November 1998 see page 5, line 28 - page 6, line 14 see sequences SEQ ID NO:11, 12, 25 ---	1-6
E	WO 98 51824 A (ABBOTT LABORATORIES) 19 November 1998 see page 5, line 8 - line 20 see sequences SEQ ID NO:11, 12, 25 -----	1-6

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP 98/04475

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6 partially (subject 1. on continuation-sheet)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/JP 98/04475

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:1; DNA encoding it;
cDNA comprising SEQ ID NO:11 or 21; vector and host cell
capable of expressing the same.

2. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:2; DNA encoding it;
cDNA comprising SEQ ID NO:12 or 23; vector and host cell
capable of expressing the same.

3. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:3; DNA encoding it;
cDNA comprising SEQ ID NO:13 or 25; vector and host cell
capable of expressing the same.

4. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:4; DNA encoding it;
cDNA comprising SEQ ID NO:14 or 27; vector and host cell
capable of expressing the same.

5. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:5; DNA encoding it;
cDNA comprising SEQ ID NO:15 or 29; vector and host cell
capable of expressing the same.

6. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:6; DNA encoding it;
cDNA comprising SEQ ID NO:16 or 31; vector and host cell
capable of expressing the same.

7. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:7; DNA encoding it;
cDNA comprising SEQ ID NO:17 or 33; vector and host cell
capable of expressing the same.

8. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:8; DNA encoding it;
cDNA comprising SEQ ID NO:18 or 35; vector and host cell
capable of expressing the same.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/JP 98/04475

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:9; DNA encoding it;
cDNA comprising SEQ ID NO:19 or 37; vector and host cell
capable of expressing the same.

10. Claims: 1-6 partially

Protein comprising sequence SEQ ID NO:10; DNA encoding it;
cDNA comprising SEQ ID NO:20 or 39; vector and host cell
capable of expressing the same.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/04475

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9800540	A	08-01-1998	US 5856136 A AU 3501197 A EP 0909318 A	05-01-1999 21-01-1998 21-04-1999
WO 9851805	A	19-11-1998	NONE	
WO 9851824	A	19-11-1998	NONE	